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AUGUST 1959

MAGAZINE OF TASTE AND SCENT THE



erfume Oils on Fungi Page 21 • Report on Griseofulvin Page 26





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VOL. 74, NO. 2

AUGUST, 1959

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FRONT COVER

A view of some of the fermenters in the Ulverston, Lan-cashire factory of Glaxe Laboratories Ltd.

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Reader Participation

Many of our readers have been good enough to tell us that they like the changes that have been taking place in our pages. Of course, such expressions of approval is music to our ears. But rather than lulling us into adopting a status quo position, we are more determined than ever to further improve, expand and balance our editorial service.

Recently we have been mailing an "Editorial Guide Sheet" to a random sample of names taken from our regular subscription list. This simple questionnaire has but one purpose: to find out what editorial features enjoy popular appeal and best serve our readers' interests in the aggregate. Actually all the recipient has to do is simply check off what he reads regularly. Space is also provided, however, for any comment the respondent cares to make.

The first-and a very modest sample mailing it was-produced a remarkable 76% return and resulted in interesting comment and suggestions. Last week we sent out a larger batch to a wider list of readers. The early returns indicate another high percentage of response and the kind of reader cooperation that would gladden the heart of any publisher.

Not the least surprising is how de-Navarre's "Desiderata" continues to be front-runner in reader popularity. It virtually possesses equal appeal to management readers as it does to chemists and technicians.

Technical articles and papers, abstracts, formulations, book reviews, etc. find great favor among research directors, chemists and others engaged in product development and improvement work.

And the Documentaries! Not only are they on top but also draw the bulk of the comment and praise, including specific suggestions of additional areas to be explored for possible Documentary treatment.

To achieve balance in a publications editorial content is no easy task. We feel the "Editorial Guide Sheet" is a step forward in sharpening editorial perspective, especially in view of the highly stimulating manner in which our readers are coming through in answering our appeal for help and guidance.

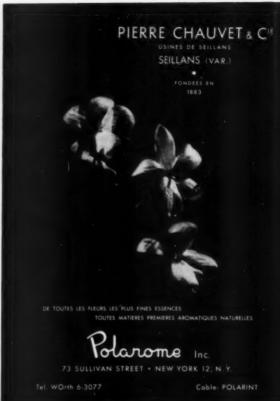
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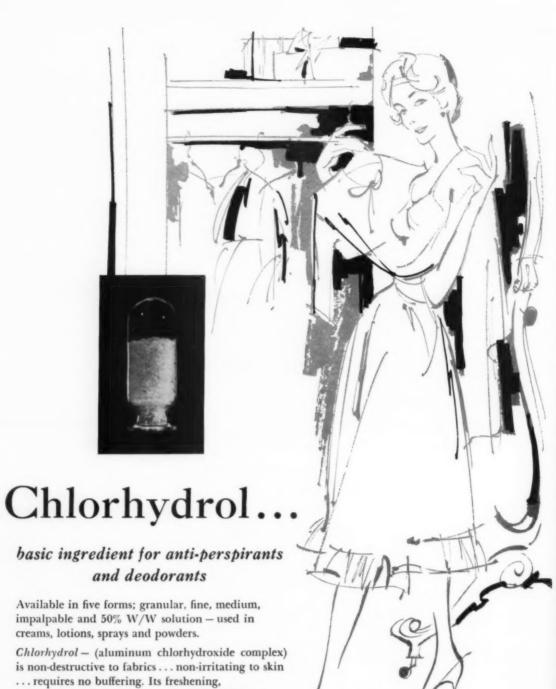
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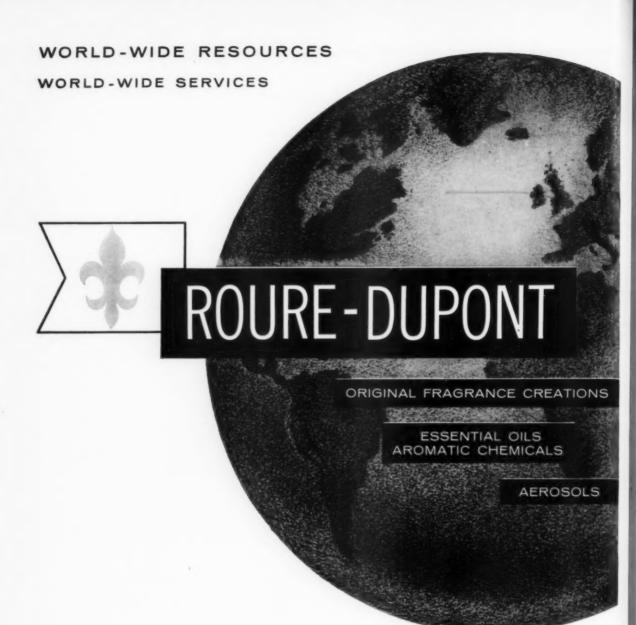
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MINUTE NEWS . . .

Teenage Brand Spending Revealed In Survey

Cosmetic Career Women Annnounce Luncheon Dates

Eyelet Specialty
Co. Completes Move

Publication, Colgate Develop Merchandising Technique

Aerosol Package Contest Planned Teenagers making brand choices often choose the more expensive or "quality" item over the cheaper one when spending the more than six billion dollars they have in yearly spendable income. So reveals Scholastic Magazine's 1959 Youth Market Consumer Survey of teen spending habits, which has just been released in a 44-page report. The survey covered 5,000 junior and senior high school students in grades 7 through 12 throughout the country. In the area of grooming products the survey reveals that more than half the girls buy their grooming and beauty aids in drug stores. Of those answering, 85% reported having a favorite lipstick brand, and 70% had a brand preference for nail polish. 40% used home permanents, and almost half use a perfume or fragrance. The average age at which boys start shaving is 14. They prefer electric shavers to safety razors by a small margin, and of those replying, 46% of senior high boys use a particular brand of shaving lotion.

Cosmetic Career Women, Inc. has announced its schedule of luncheon-meetings for the coming season. They will be on the following dates: September 29, December 8, February 2, and April 5. The guest speaker at the September 29 luncheon will be Dr. Ernest Guenther, Vice-President and Technical Director of Fritzsche Brothers, Inc.

The Eyelet Specialty Company, International Silver Company's newest division, has just completed the move of its entire U.S. manufacturing facilities to International's Factory A-J in Wallingford, Conn. One of the country's leading producers of cosmetic containers, Eyelet became a division of International Silver in January 1958. The move to Wallingford, according to Steven J. Clark, founder and General Manager of the Eyelet Specialty Division, provides a needed opportunity to expand and will enable Eyelet to improve its position in the cosmetic industry. The Eyelet Specialty Company was founded in 1923 in Wolcott, Conn. and moved to Waterbury, Conn. five years later. There it grew under the leadership of Mr. Clark to its present position as a major supplier of lipstick cases to cosmetic firms. A wholly owned subsidiary of Eyelet in Canada is Canadylet Closures, Ltd. in Barrie, Ontario.

Colgate-Palmolive signs featuring a back-to-school promotion on toothpaste have been bound into the current issue of Variety Store Merchandiser, publication in the \$4 million variety field, as a merchandising service to variety stores. The signs—7-inches by eleven on 10 point board stock—are perforated and ready for instant use at point of purchase.

The Eighth Annual Aerosol Package Contest will be held in conjunction with the 46th annual meeting of the Chemical Specialties Manufacturers Association at the Mayflower Hotel, Washington, D.C., December 7-9, 1959. There will be several classes of entries, and the contest is open without fee to any brand owner or marketer of aerosols and pressurized packages. Awards will be made on the basis of general sales appeal of the packages. Rules of the contest and entry blanks will be sent upon request to the CSMA, Aerosol Awards Committee, 50 East 41st St., New York 17, N.Y.

Knox Purchases Buck Glass

Express Tariffs Filed; Incentive Rate Reductions

Silicon Hair Curlers Proven Dangerous To Beauticians

Industry People

Knox Glass Inc. of Knox, Pa., completed in July purchase of 100% of the stock of Buck Glass Company, Inc., of Baltimore. Purchase price was not revealed. News of the transaction was made public jointly by Dr. Arthur W. Wishart, president of Knox Glass, and Royden A. Blunt, president of Buck. Terms of purchase previously had been agreed upon by Knox management and Mr. Blunt who represented Buck shareholders. Following its acquisition of the stock, Knox Glass elected the following to serve as directors of Buck: Dr. A. W. Wishart, chairman and chief executive officer; Royden A. Blunt; Clarence R. Deible; A. W. Lansberg, treasurer and controller of Knox, and W. A. Seger.

Railway Express Agency has announced its filing with the Interstate Commerce Commission of incentive tariffs providing for substantially reduced rates, effective September 8, on individual prepaid small shipments of specified commodities when picked up in bulk lots of 300 pounds or more at one time from one shipper at various origin points. The tariffs extend the unique form of incentive rates pioneered by the agency in 1955, predicated on reductions in per shipment costs resulting from the increased quantities thus received from a shipper, William B. Johnson, President, said. Incentive tariffs, previously effective, apply from listed origin cities on other commodities. They include: deoderants, disinfectants, and insecticides; drugs, medicines, and toilet preparations.

Silicon hair curlers may produce an invisible but terribly painful skin disease among hairdressers, two University of Pennsylvania dermatologists warned recently. Writing in the August 8 Journal of the American Medical Association, Drs. Walter B. Shelley and Donald M. Pillsbury said the disease consists of excessively sensitive fingertips, although the skin shows no sign of disease. The sensitivity is due to tiny particles of silica which become embedded in the top layer of the skin, irritating the sensory nerve endings. The particles rub off silica or sand-coated hair curlers, which have replaced plastic curlers in many beauty shops. The widespread use of these curlers suggests that such an invisible skin disease "may become common among beauticians unless efforts are taken to eliminate this new occupational hazard," the doctors said.

Robert D. West is now aerosol formulation chemist at Union Carbide Chemicals Company. He will formulate and test new aerosol products for Carbide's Ucon propellant customers. . . . John V. Grace, former assistant sales manager of Prince Matchabelli Inc., has been appointed the company's eastern regional manager. . . . Dr. Albert H. Cooper has been appointed director of research and development for the Waverly Chemical Company, Mamaroneck, N.Y. . . . Lorenzo De la Vega is new advertising manager-International Division of Shulton, Inc. John C. Tobin has been made a product manager at Shulton; he will handle the marketing and merchandising program for the company's women's fragrance products. . . . Walter H. Dunnican is manager of the Lehn and Fink Products Corporation's package engineering department. He was formerly packaging engineer for the Dorothy Gray Division. . . . Joseph M. Hall is new manager of the Canco division coil stock plant in Hammond, Indiana, of the American Can Co. . Andrew C. E. Peasco has been appointed industrial sales manager of .Eleanore H. Peitsch, a literature scientist at Smith Kline & French Laboratories, is the first woman recipient of the company's Walter G. Karr Fellowship for post-graduate study. . . . Dr. George F. Reddish has relinquished his active duties as chief bacteriologist of the Lambert-Hudnut Manufacturing Laboratories to devote full time as professor of Microbiology and Public Health of the St. Louis College of Pharmacy and Allied Sciences. He will continue as a consultant to Lambert-Hudnut.

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Human Placenta Extract

It is easy to shrug off the value of a material like placenta if you don't check into it thoroughly. But after you read the scientific literature—not the advertising type of article so often found in some European contemporary trade papers—you find that placenta, particularly of human origin, contains many goodies, passed over too quickly.

The Europeans have been making placenta extracts, bovine and human, in many types. Water soluble lyophillised material seems to be preferred here, although oil solutions, glycerol and glycol extracts are made not to mention Filatov extracts which are also available. Two companies in the U.S. are offering a placenta extract, the one standardized on nitrogen, the other on a phosphatase activity.

We now find a new source, using French material with several times the phosphatase activity of U.S. material, as a water extract, standardized, available from stock. Human placenta is the source of the extract. Best news yet, it is cheaper than what you have paid for bovine material based on phosphatase activity.

It is believed that human skin "accepts" human placenta extracts more readily than bovine extracts.

Mechanical Nose

For about a century, man has tried to reduce the odor and taste of things to a reproducible equation. Even in the present day, a system of odor classification by Crocker and co-workers has been elaborated.

Now comes Murray Berdick of Evans Research who has collaborated with D. A. M. Mackay in developing a mechanical nose of great discrimination and fantastic sensitivity. You can even distinguish between the kinds of whiskey in human breath. This might be a useful scientific lab tcol, but it will not be popular with "the people" because it will take the glamor out of the more ethereal things in life, like the perfume a woman is using.

New Sugar Esters

A new series of alkoxylated sugar ester of fatty acids has been made experimentally. Original emulsions made, look quite good. Vegetable cils, which ordinarily give coarse textured solid creams, produce smooth, glossy emulsions. High wax content creams appear to result in very soft creams. More work is necessary to find out just how useful these materials are.

Notes

G. P. A. gave us a nice front page spread on our recent Pharmaceutical Cosmetics documentary. Thanks G. P. A. . . . Eight aldehydes have been identified in rose oil by workers in Bulgaria. Don't overlook ethylene oxide as a sterilizing agent for many materials hard to free of contamination. . . . Glycerol formal has been suggested as a water soluble solvent with good solvent properties for many substances during toxicity testing according to the J. PHARM. PHARMACOL., II, 150, 1959. . . Among a group of twenty essential oils tested, peppermint, cinnamon, clove, lemon and caraway oils were most bactericidal . . . Only anise oil

failed to show bacteriostatic properties. . . . The use of ultrasonic waves on vanilla beans increased the vanillin and oleoresin content from 10 to 35 per cent.... The Japanese Perfumery and Flavoring Associations Journal Koryo No. 51 has a fine article on the application of sorbitol in the pharmaceutical field, while No. 52 lists formulas for tobacco flavors, such as Camel, Players and eight others; these are in English but the text is in Japanese. . It's interesting to read Brown Bolte's prediction given before the Proprietary Association that 400 new drug products would be introduced in 1959 and that 95 per cent of them will have disappeared in a year-yet new products are a must if you are to stay in business. . . . A new ear wax softening formula contains a triethanolamine oleyl polypeptide surfactant dissolved in propulene glycol containing chlorobutanol (ARCH. DERMATOL., 79, 651, 1959).... Compounds of urea and essential fatty acids do not become rancid very easily and can be used in foods (U. S. Patent No. 2,785,060) - maybe cosmetics too? ... Mentha sachalineusis is claimed to produce an oil containing 75 per cent of L-menthol. . . . U. S. Patent No. 2,876,164 covers the use of a fat-free soybean flour in cosmetic preparations. . . . Unlike so many articles on the subject, Bassiri lists aromatic substances found desirable in polyethylene containers. Some 125 materials are mentioned (PARF. KOSMETIK, 39, 483, 1958). . . . A German Patent No. 1,033,829 claims coverage for the use of zinc carbonate which increases germicidal properties of soaps containing bithionol, hexa-



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cholorophene and related compounds along with the halogenated salicylanilides and TMTD. . . . Another German Patent uses alginic acid or its propylene glycol monoester in 20 to 30 per cent hydroalcoholic solution as an electric preshave. . . . Oxidized fish oils are toxic to albino rats or if applied externally, death occurring in seven to ten days. (The obvious question is, what is good about fish?) . . 3-methylthiopropanol, (methional) is suggested as a food flavor. . . . Got a kick out of Consumer Reports story on the Pakistani product OTOGEN which restores beauty, vigor, hair color; prevents fading charms and if allowed to stand in a drinking glass, in time the glass becomes almost break proof. This only proves that all great discoveries are not made in either the United States or Russia. . . . Steve Goode (Rita Chemicals) is now importing human placenta extracts with standardized phosphatase activity....

Book Review

CHOLESTEROL, by D. Kritchevsky, John Wiley and Sons, Inc., New York 16, N.Y. 1958. 291 pages, indexed, size $9\frac{1}{2}$ x 6 inches. Price \$9.75.

The data on which this book is based, has been gathered by the author for his personal use, to overcome a lack of "centralized source of information." All this is accomplished in seven chapters which cover the chemistry, biosynthesis, absorption and transport, metabolism, analysis and the problem of blood cholesterol including the diseased state.

This book together with Truter's work on Wool Wax gives workers in this industry a wide coverage of chemistry of lanolin and cholesterol. *M. G. deNavarre*.

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1345 SKIN BLEACH

Q. We would greatly appreciate your opinion on the value and effectiveness of Hydroquinine and some of its derivatives, as bleaching agents for the skin in colored people, when incorporated into facial cream. A. K. deM., Fla.

A. It is our oninion that derivatives of hydroquinone used for bleaching skin should be used only by qualified doctors and no one else. The man who first discovered the effectiveness of these products was most anxious that they never get into general usage, and we cannot help but agree with him. We regret that we find it impossible for us to suggest the use of these materials for the purpose outlined in your letter.

1346

Q. Could you please give us a list of articles published on the compatibility of materials with aerosol products. R. K., Mexico. A. I would suggest that you write to Dr. Carl Bergwein at Dragoco, Inc., 250 West Broadway, New York 13, New York, and also to Victor DiGiacomo at Givaudan-Delawanna, Inc., 321 West Forty-fourth Street, New York 36, New York, and to Vincent DeFeo, Dodge & Olcott, Inc., 180 Varick Street, New York 14, New York, as well as to Mr. H. J. Amsterdam, van Ameringen-Haebler, Inc., 521 West Fiftyseventh Street, New York 19, New York.

1347

Q. Could you give us an approximate estimate as to the number of lipsticks sold annually in the United States. J. P., Fla.

A. There is no known record of how many lipsticks are sold annually. I have heard estimates of 200 to 500 million but that is as close a guess as anyone has made. As for further statistical information regarding this field, you might want to check the Fawcett Survey or the Good Housekeeping Survey, both made by the magazines of the same names.

From time to time suggestions have been and will be made in this magazine with respect to processes, devices, materials, appliances, equipment and the like. It is not practicable for the writers and editors to have a patent search or examination made in connection with each such suggestion. Our readers are, therefore, requested and indeed urged to determine for themselves whether any patent or other right will be violated before acting on any such suggestion.

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Check List of Best Selling Technical Books

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- □2. PERFUMES AND THEIR PRODUCTION. By E. S. Maurer. This is the first text of its kind in the English language to give a complete picture of the perfumer's training, and methods of working. In Part I the reader is offered a complete picture, not only of formulations, but of the entire scope and organization of the perfume industry. Part II is a systematized discussion of all the commonly used perfumery isolates and synthetics. Practical hints on utilization of most of these materials are included, together with notes on their specific applications, blending properties, and other functions. 313 pages. Price \$6.50.
- □3. PRESSURIZED PACKAGING (AEROSOLS). By Alfred Herzka Jack Pickthall. Although technical problems occur with all types of packages, those which arise with pressurized packages are many and complex. This reference book, by two recognized authorities deals with propellants, containers, valves, filling methods, laboratory procedures, emulsified systems, and perfumes. There is a complete section containing more than 200 formulations, including foods, insecticides, cosmetics, paints, and numerous other products. 400 pages. Illustrated. Price \$12.00.
- □4. PERFUMERY SYNTHETICS AND ISOLATES. By Paul A. Bedoukian. This carefully compiled volume meets the genuine need for authoritative data on perfumery synthetics. It embraces the history, chemistry, physical and chemical properties, manufacture, uses, and other pertinent data of the principal perfumery compounds; and covers the important perfumery synthetics. A complete index adds to the value of this important work. 488 pages. Price \$9.25.
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- □6. COSMETICS—THEIR PRINCIPLES AND PRACTICES. By Ralph G. Harry, discussed the skin, its nutrition and scientific care; the hair, its proper grooming, the physio-chemical problema involved in its washing; the teeth and their care, covering the present status of different dentrifices, and the luster-producing properties of ingredients. Much of the information has its source in the research activities of its author, embracing chemistry, dermatology, and microbiology. 786 pages. Illustrated. Price \$17.25.
- □7. INTERNATIONAL ENCYCLOPEDIA OF COSMETIC MATERIAL TRADE NAMES. By Maison G. deNavarre, brings you reference data you will turn to constantly... the most complete listing of all the materials of the world used in cosmetic manufacture... including quick concise descriptions of approximately 4,000 materials... the names and addresses of the suppliers... and a very useful cross-index of the materials and their uses. You will use it when seeking new materials, or substitutes for those you may now be using. 400 pages. Price \$7.50.
- ■8. HANDBOOK OF COSMETIC MATERIALS. (Their Properties, Uses, and Toxic and Dermatologic Actions). By Leon Greenburg and David Lester. Contains alphabetical listing, with frequent cross references, of information on approximately 1,000 substances. For each compound gives: formula (including collateral names), properties, toxic action, dermatological action. Exhaustive bibliography. Essential for manufacturing chemists, cosmetic industry, dermatologists, allergists. 467 pages. Price \$12.75.
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The Action of Perfume Oil Vapors on Fungi

The following article deals with the activity of perfume oil vapors against a variety of pathogenic and non-pathogenic fungi. The action of 100 perfume oils was tested against growing cultures of 6 fungi. All the organisms were cultivated in Sabauraud dextrose agar and broth for four days at room temperature.

JASPER C. MARUZZELLA, JERRY BALTER, AND ALEXANDER KATZ*

The antibacterial properties of perfume oils were first demonstrated in 1924 by Dyche-Teague (1) on a mixed bacterial culture obtained from the respiratory tract of man. This work confirmed in that same year by Bryant (2) who used as the test organism a pure culture of B. coli communis. Both investigators employed the phenol coefficient method in their studies. Recently Maruzzella and Henry (3) in a rather extensive survey examined 100 perfume oils not only for antibacterial activity but also for antifungal properties. These investigators used the filter paper disk method and 20 test organisms and reported that 70% of the perfume oils tested possessed microbicidal activity, the fungi being almost twice as susceptible than the bacteria.

Since perfumes are essentially associated with the vaporous state a study of the antimicrobial activity of perfume oil vapors would be of great value. Interestingly enough in his original paper Dyche-Teague conducted some experiments on the action of alcoholic perfume vapors but obtained inconclusive results. This report therefore deals with the activity of perfume oil vapors against a variety of pathogenic and non-pathogenic funci.

Materials And Methods

The action of 100 perfume oils was tested against growing cultures of 6 fungi. These test organisms were: Saccharomyces cereviseae (ATCC 7921), Aspergillus niger (ATCC 6277), Gibberella fugikuroi (NRRL 2284), Candida albicans (MY-907-57), Rhodotorula mucilaginosa

(Coll. No. 4676), and *Geotrichum candidum* (Coll. No. 4762). All of the organisms were cultivated in Sabauraud dextrose agar and broth (Difco) for 4 days at room temperature.

The method used for testing the presence or absence of antifungal activity of the perfume oil vapors was as follows. Approximately 8 ml. of Sabauraud dextrose agar was poured into sterile Petri dishes and allowed to solidify. The surface of the agar was then streaked with 0.5 ml. of a 4 day old broth culture of the organism. Filter paper disks (6.35 mm. in diameter) were previously saturated with the perfume oil to be tested and placed in the center of the inner surface of the Petri dish top. Thus when the dishes were inverted and incubated the saturated disk would be at a distance of about 8 mm. from the surface growth of the organism. All dishes were incubated for 3 days at room temperature. The presence of a definite zone of inhibition on the surface of the agar was indicative of antifungal activity of the vapor. The diameter of the zone of inhibition was measured to the nearest millimeter by means of a metric ruler and an illuminated Quebec colony counter. All dishes were conducted in quadruplicate. Some perfume oil vapors allowed no growth to occur on the entire dish and such dishes were recorded as 90 mm. (the inside diameter of the entire Petri dish).

Results And Discussion

Of the 100 perfume oil vapors tested 18 were found to possess no antifungal activity while the remaining 82 showed activity on at least one of the 6 test organisms. The perfume oil vapors with antifungal activity together with their zones of inhibition are found in Table 1. The

^{*} Long Island University Biology Department, Brooklyn, N.Y.

Oil Vapors	S. cere-	A. niger	G. fugi-	C. albi-	R. mucila-	G.
	viseae		kuroi	cans	ginosa	dum
Allspice	20	35	35	30	41	33
Almond S	4	50	90	15	90	90
Apple Blossom No. 200	0	10	20	19	5	0
Apple Blossom B.S.	0	0	0	0	15	0
Arabian "N"	0	20	0	0	12	0
Ashton Villa No. 6	0	0	0	0	15	0
Bay Rum Essence	17	25	25	18	35	0
Blue Bell Bouquet	0	30	25	25	20	10
Bluestone Bouquet	15	40	30	15	40	20
Bouquet No. 21	0	30	22	20	30	20
Bouquet No. 22	0	0	0	0	20	0
Bouquet 821 Lemon Odo		25	35	25	65	30
Bouquet B.L.S.	20	45	25	20	45	30
Carnation No. 1162	0	20	20	0	25	0
Chypre French Type	0	0	0	0	20	10
Cinnamon	25	50	35	40	37	40
Citrus Odor No. 50B	20	20	20	23	40	30
Cologne American	10	20	10	15	45	15
Colognial Bouquet Compounded Fruit Odor	0	20	10	0	20	60
No. 1285	20	50	25	12	50	10
Carylopsis No. 602	0	20	15	0	20	10
Carylopsis No. 604	0	20	15	0	22	0
Crab Apple Blossom	0	10	0	0	12	10
Eau de Quinine M.O.	0	20	10	0	25	10
Elders Buds	0	20	5	30	20	15
Evergreen Bouquet	0	0	5	0	0	0
Florida Water	20	20	15	0	25	15
Fragipanni	0	18	15	0	20	20
Gardenia No. 1500	0	15	20	0	0	0
Gardenia G.H.	0	0	5	0	0	0
Gardenia J.M.	0	20	12	0	20	0
Gardenia "S"	0	25	15	0	15	0
Geranium Bouquet	0	5	5	0	40	20
Helliotropine	0	30	20	0	21	0
Honey Suckle	5	10	15	0	15	0
Hyacynth "N"	0	20	5	0	35	20
Jasmine No. 11347	0	25	20	0	12	0
Jasmine "N"	20	25	25	10	17	20
Jasmine Ordinary	0	10	0	0	12	10
Jockey Club	0	15	20	0	20	0
Lavender "Y" ·	0	25	0	0	65	0
Lavender Bouquet D.R.	0	0	0	0	20	0

Table 1. Inhibitory Activity of Perfume Oil Vapors on Fungi Table 1. Inhibitory Activity of Perfume Oil Vapors on Fungi

011 17	8.	A.	G.	C.	R.	G.
Oil Vapors	cere- viseae	niger	fugi- kuroi		mucila- ginosa	dum
Lemon Bouquet No. 58	20	50	30	22	43	30
Lemon Bouquet No. 62	0	5	5	0	20	10
Lemon L.M.	0	0	0	0	30	0
Lilac Roval	0	20	10	0	0	15
Lilac Water	15	25	20	20	25	18
Lilas Blanc	0	32	20	15	35	20
Lilas Blanc L.S.	0	40	30	0	25	20
Lilas Vegital Lilly of the	5	30	30	10	30	10
Valley Supreme	0	40	20	15	30	40
Lotus Blossom	0	15	5	0	23	0
Magnolia	0	5	5	0	0	0
May Apple Blossom	0	10	12	0	10	0
Mille Fleurs	0	20	10	10	35	0
Mimosa No. 11548	0	12	10	0	0	0
Mint Bouquet No. 122	0	0	0	0	35	0
Narcissus	0	30	10	0	0	0
Neroli Artificial	0	20	0	0	25	0
Neutralizer F. A.	25	40	30	27	31	25
New Mown Hay No. 100	0	15	15	0	0	0
Orange Blossom "N"	0	35	20	25	25	0
Oriental Bouquet						
No. 225	15	30	15	0	31	0
Palma Bouquet	0	30	10	22	20	20
Rose No. 81412						
Otto Type	0	15	20	0	15	10
Rose D.B.	0	0	3	0	20	0
Rose Bleue	0	20	20	15	25	0
Rose Briar	0	23	15	0	17	5
Rose Gladis	0	0	5	0	15	15
Rose Odorata	0	25	10	0	20	0
Rose Red	0	35	15	0	25	18
Roxul Bouquet	0	15	10	15	15	0
Spring Flower Bouquet	0	35	15	0	10	0
Sweet Grass	0	20	15	0	30	20
Sweet Pea	0	16	20	0	10	0
Trefle L.H.	0	5	10	0	30	0
Tuberose	0	25	10	0	15	0
Violet No. 257	0	25	5	0	0	0
Violet "F"	0	20	0	0	0	0
Violet F.D.	0	25	10	20	30	0
Wisteria	0	30	5	0	28	12
Ylang Ylang Artificial	0	5	0	0	0	0

perfume oil vapors with no activity were: Chypre 66D, Cologne "F" European Type, Eau de Cologne "S" Fougere No. 966, Jasmine No. 679, Osheana, Pine Needle Bouquet No. 400, Pine Needle Bouquet V.H., Pine Bouquet Supreme, Pine Bouquet Swiss Type, Rose No. 225, Rosesol, Russian Leather, Sandalwood A-3, Vanilla K-600, Violet No. 23, Violet de Luxe, and Violet Supreme.

It is interesting to note that in the above mentioned work of Maruzzella and Henry they used the identical 100 perfume oils tested in this study. Furthermore in the direct contact method they found that 90% or more of the perfume oils were effective in killing each of the 10 fungi tested (among the 10 fungi were: Saccharomyces cereviseae, Candida albicans, and Aspergillus niger). In this investigation it may be seen (from Table 1) that 16% of the perfume oil vapors were effective against S. cereviseae, 70% against A. niger, 67% against Gibberella fugikuroi, 26% against C. albicans, 70% against R. mucilaginosa, and 38% against G. candidum. The vapors of the following perfume oils showed the greatest activity against the organisms tested: Almond S, Cinnamon, Lemon Bouquet No. 58, Allspice, and Bouquet B.L.S.

The important implications of these findings need not be emphasized when one considers how extensively perfume oils are incorporated into various articles applied externally for ornamental and hygienic purposes. It is not unreasonable to assume that the more extensive use of those perfume oils which possess marked antifungal vapors might afford a certain degree of protection

against fungal infections of the body. Indeed the addition of certain perfume oils to medicaments applied externally might enhance the antimicrobial properties of the product.

These findings do not give any clues as to how rapidly the vapors of the perfume oils might kill various organisms or whether the vapors possess antibacterial properties. These areas are now being investigated.

Summary

The in vitro antifungal activity of perfume oil vapors was investigated. Data presented show that 82 of the 100 perfume oil vapors studied possess antifungal activity against at least 1 of the 6 test organisms.

The vapors of 18 perfume oils were found to have no antifungal properties.

The most potent vapors were possessed by perfume oils of: Almond S, Cinnamon, Lemon Bouquet No. 58, Allspice, and Bouquet B.L.S.

In general perfume oil vapors possess lower antifungal activity than the perfume oil itself.

Acknowledgements

The authors wish to extend their thanks and appreciation to Magnus, Mabee, & Reynard, Inc., New York, N.Y. for their generous supply of all of the perfume oils.

- Dyche-Teague, F. C., Perfumery Essent. Oil Record, 15, 6 (1924).
 Bryant, J. J., ibid., 15, 426 (1924).
 Maruzsella, J. C., and Henry, P. A., J. Am. Pharm. Assoc., 47, 471 (1958).

Stability Prediction In The Pharmaceutical Industry

EDWARD R. GARRETT*
The Upjohn Company

Introduction

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The pharmaceutical and cosmetic industry is legally and morally obligated to market preparations that will maintain their label values and initial appearance for the duration of their market or shelf life.

Physicochemical and statistical procedures which permit prediction of stability and optimum composition from accelerated studies should allow release of products

- a year or more ahead of standard operating procedures to give the public early benefit from modern health research and to establish priority in competitive fields.
- which can compete with the market, e.g., no refrigeration labels.
- with the most economic use of expensive components.

Prediction of Thermal Stability

The Physicochemical Basis.—Thermal degradation should follow the Arrhenius' relation with absolute temperature (T):

$$k = Ae^{-\Delta H_a/RT}$$
 (1)

where k is the specific rate of degradation of the pertinent component, R is the gas constant (1.987 calories degree $^{\rm a}$ mole $^{\rm a}$), A is a constant associated with the entropy of the reaction and/or collision factors, and $\triangle H_a$ is defined as the heat of activation.

The logarithmic form of equation (1):

$$\begin{array}{l} \log \, k \, = \, - (\Delta H_{\rm a}/2.303 R) \, (1/T) \, + \, {\rm constant} \\ = \, - S/T \, + \, P \end{array} \eqno(2)$$

shows that any value proportional to the specific rate, k, would permit evaluation of the slope of the plot log k vs. 1/T and thus prediction of stability at shelf temperatures from accelerated temperature studies should be practical.

The degradation or some property of the degradation should be followed as a function of time and this function should be linearized. The slopes of such linear plots may be used as estimates of the specific rates (k). The reproducibility of such a degradation rate function at the various elevated temperatures would validate the use of such functions in the prediction of degradation rates at lower temperatures (1).

The order of the degradation rate of a component in a complex preparation is defined as the power, n, of the concentration proportional to the rate of degradation:

$$dy/dt = -ky^n$$
 (3)

where y is the concentration of the degrading component to be studied. In all cases of thermal degradation studied so far either, (1-3) (6)

$$n = o \text{ where } y = y_o - k_o t$$
 (4)

$$n = 1$$
 where $\log y = \log y_o - k_l t$ (5)

*Presented at the Third Stevens Symposium on Statistical Methods in the Chemical Industry, Jan. 1939, Hoboken, N.J.

have served satisfactorily to characterize the loss of initial assay (y_o) with time (t) within the errors of assay. Analogous procedures can be developed, however, for the other possible values of n. Antocatalytic degradation, however, may need special treatment.

The Statistical Basis. (2) (3) (6)—Assignment of the appropriate order of degradation rate can be generally made on the basis of inspection. However, a rough statistical test would be to fit the data by least squares to both zero order (equation 4) and first order (equation 5) plotting and determine the residual variance, σ^2 , about both regression lines. The variance, σ^2 , about the regression concentration on time, may be compared to the variance, $\sigma'_y{}^2$, derived from the variance $\sigma^2_{\log y}$ about the regression log concentration on time by

$$\sigma'^{2}_{y} = (2.303 \text{ y})^{2} \sigma^{2}_{\log y}$$
 (6)

Whichever variance, σ^2_y or $\sigma'_{y}{}^2$ is in excess may be assumed to be derived from the least valid linear relation. The factor, $\overline{y}_{\!\!y}$ in the above equation may be estimated from the average concentration value during the rate study.

In several studies, the component has had an initial pseudo zero order degradation which subsequently became first order. For purposes of prediction of time of maintenance of a minimum concentration value, the zero order portion of the plots frequently need only to be considered.

Since many drug assays are based on biological methods with relatively large inherent error, it is important that statistical techniques be employed to determine the best estimates of the rate constants, assays, and rate predictions in these cases.

Interestingly, the estimates of variation about regression in the studies conducted can be completely assigned to the errors in biological assay. The agreement in estimates of error from fitting the concentration by assay to the appropriate zero or first order plot and from

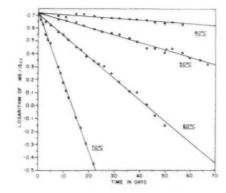


Fig. 1, First order plots of the thermal degradation of thiamine hydrochloride in a liquid multivitamin preparation (A); logarithms of concentration (mg./15 cc.) against time in days.

independent statistical studies of assays of randomized dilutions of underraded materials was excellent.

An example of data fitted by least squares to a first order plot of equation (5) is given in Fig. 1 for the thermal degradations of thiamine hydrochloride in a liquid vitamin preparation. The statistics derived from such fitting are estimates of the slope, k, and intercept, log y_{o} , values as well as the estimates of error in the slope, σ_k , and about regression, $\sigma_{log\ y}$ or σ_y , assignable to assay error.

The logarithm of the slopes of these temperature studies against 1/T as per equation (2) is given in Fig. 2 as also fitted by least squares. The circles represent the standard deviation of the experimental log rate constant and the rectangles represent the standard deviation of a predicted log rate constant. The horizontal lines represent the 95% confidence limits of experimental and predicted log rates.

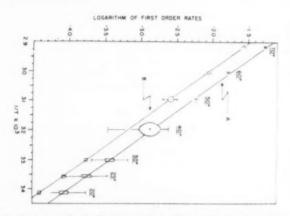


Fig. 2. Arrhenius' plots for thiamine hydrochloride. Plot of the logarithm of the slopes of first order plots (in days) against the reciprocal of the absolute temperature (T) for the thermal degradation of thiamine hydrochloride in liquid multivitamin preparations A and B. The circles represent the standard deviation of an experimental log rate and the rectangles the standard deviation of a predicted log rate. The horizontal lines represent the 95% confidence limits of experimental and predicted log rates.

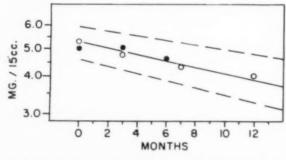


Fig. 3. Verification of prediction of thiamine hydrochloride stability at room temperature. The solid line is the predicted thermal degradation rate of thiamine hydrochloride in liquid multivitamin preparation A at 30°. The dashed lines encompass standard error in predicted values and the standard error or a single assay. The open circles are data from preparation A and the closed circles are data from a similar preparation A.

The log k values have not been weighted in these Arrhenius plots. Weighting by assay error would have given greater significance to the higher temperature values which, it can be argued, would give the more valid estimate of $\triangle \mathbf{H}_a$. However, since extrapolation is the desired end, the experimental values adjacent to those to be estimated may be more significant chemically.

Thus, the mode of weighting is still left open for a question in philosophy.

The data fitted by the statistical methods of least squares to the Arrhenius equation (2) permit estimates of the standard error, σ_a , of the slope S, the constant P, and the standard deviation, $\sigma_{\log k}$, of the logarithm of the rate constants. The values of P and S may be substituted into equation (2) to predict the log k at a lower temperature. The estimated error in prediction, σ_p , of a log k at any absolute temperature, T_p , may be based on the equation:

$$\sigma_{\rm p} = \sigma_{\rm log~k} \sqrt{({\rm N}+1)/{\rm N} + [1/T_{\rm p} - (1/T)_{\rm a}]^2/\Sigma} [1/T - (1/T)_{\rm a}]^2 \quad (7)$$

where N is the number of temperature studies, $(1/T)_{\,\rm a}$ is the mean of the reciprocals of the absolute temperature at which the rates were evaluated and $\Sigma[1/T-(1/T)_{\,\rm a}]$ are the sums of the squares of the deviations of the reciprocal temperatures from their mean.

The degrees of freedom for σ_p are N-2 and 95% confidence limits may be estimated from $t\sigma_p$. The relatively large decrease in t for the increase in numbers of temperature studies (N) from 3 to 4 may justify the cost of an additional rate study at another temperature. In general, increased confidence in predicted values from increased numbers of temperature studies must be balanced by the necessary economic considerations.

Prediction and Its Verification

The predicted rate constants, k_o or k_1 , obtained from the Arrhenius extrapolation are substituted into the appropriate zero or first order equations. The estimated years, t_m , of maintenance of the minimum assay desired, y_m , can be based on the expressions:

$$t_m = (y_0 - y_m)/k_0$$
 (8)

for the pseudo-zero order rate and

$$t_m = (\log y_o - \log y_m)/k_1 \tag{9}$$

for the pseudo-first order rate.

The proof of the pudding is in the eating. An example of such proof is the typical Fig. 3, a plot of the experimental assay values against time for the preparation kept at room temperature. The solid line represents the predicted thermal degradation at the given temperature. The dashed lines encompass the standard error in the predicted thermal degradation and the 95% confidence limits of a single assay.

Fig. 4 is another such example for folic acid in a liquid multi-vitamin preparation maintained at room temperature. The open circles represent the experimentally obtained assay values on the preparation previously studied for prediction. The closed circles are for a replicate preparation, prepared at a different time but of the same formula. The half-closed circles represent data from a modified preparation with increased initial concentrations of folic acid and other vitamin components. The predictions of stability of the latter were based on the detailed studies of the first preparation.

Additional proof of the validity of and references for these techniques are in the literature (1) (2) (3). Recently, H. A. McLeod, O. Pelletier, and G. A. Campbell¹⁰ of the Food and Drug Laboratories, Department of National Health and Welfare, Ottawa, Canada, the Canadian counterpart of our own Federal Drug Administration, have repeated these studies on randomly chosen multivitamin preparations and have confirmed the general validity and general usefulness of these procedures. Their motivation was obviously to influence Canadian pharmacy to predict effective shelf life with known precision so that products would not stay on

retail shelves past the date of maintenance of minimum potency. For the purpose of promoting acceptance by the

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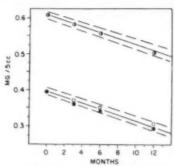


Fig. 4. Verification of prediction of folic acid stability at room temperature. The solid lines are predicted thermal degradation rates of folic acid in liquid multivitamin preparation A at 25°. The dashed lines encompass standard error in predicted values and 95% confidence of a single assay. The open circles are data from preparation A, the closed circles are data from a similar preparation B, and the half closed circles are data from a modified preparation C with increased initial concentration of folic acid and other vitamin components.

Canadian pharmaceutical industry of use of these procedures in a routine manner, they have spelled out the statistical treatment step by step in their article.

Questions of Design and Practice

Since time is frequently "of the essence" in these studies, the sampling design is necessarily arbitrary and sequential, i.e., subject to "seat-of-the-pants" redesign. Economics of assay also needs to be considered. Possible bulk drug variations should be evaluated by balanced

In general, twenty replicate vials of material of unknown degradability are placed in 70°, 60°, 50° and 40° constant temperature mineral oil baths with a preliminary daily assay schedule for 70°, every other day at 60°, and twice weekly for 50° and 40°. Controls at refrigerated temperatures are also run weekly. These samplings are economically adequate for most thermal solvolytic decompositions but times of sampling may be subject to change on the basis of early results. The use of replicate vials is important to the design, rather than the taking of aliquots of one lot of the preparation at each temperature. It is also recommended that, whenever feasible, an exact amount needed for an assay be measured out prior to the study to reduce bias with time of sampling.

Statistical studies of microbiological assay variation have shown a day-to-day variation with such assays (7). This time bias in biological assay may even introduce a higher error into estimates of stability by room temperature studies than would be inherent in prediction from accelerated temperature studies. In the latter cases, the time scale is compressed so that the reliability of the biological assay may be enhanced and the variation in the comparison standard may be lessened.

Experience has shown that slight modification of vehicles and composition do not significantly affect the rate of change of degradation rate with temperature (3). Thus it may be practicable in many cases to predict on the basis of one elevated temperature and the Arrhenius slope. (See the Arrhenius plots of one component for two different pharmaceutical formulae in Fig. 2 where slopes are the same but intercepts differ.) This type of prediction may serve as an efficient control procedure as when a batch of one component is introduced from a new source, is increased in amount, or a manufacturing process is modified. This procedure is not applicable to two different components; Arrhenius slopes of such will differ even in the same preparation.

However, when the vehicle or formulation is entirely new, the rate of change of degradation rate of a component with temperature is not the same in both vehicles. Valid prediction is not possible from comparison at only one elevated temperature. The slopes of the Arrhenius equation must be determined anew.

The use of these physicochemical procedures for prediction of stability must be considered in the light of the controlling mechanisms of degradation (3). In the previous discussion, components were considered that most probably degrade by solvolytic processes; i.e., reactions in solution and their heats of activation as per Arrhenius' slope are generally in the range 10-30 Kcal./mole. Thus advantage may be taken of significant increases in rate with temperature. However, if diffusion or photolysis are the rate determining steps, the heat of activation is only of the magnitude 2-3 Kcal./mole and little advantage is gained by accelerated temperature studies in prediction since the temperature effect on rate is small. In some cases, such rates may be accelerated by increases in pressure or light intensities.

Frequently the thermal degradation of polyhydroxylic materials and the subsequent effect on other components are of interest. However, it must be realized that the heats of activation for such pyrolysis are frequently of the magnitude of 50-70 Kcal./mole. Thus rates of degradation which may be great at elevated temperatures may not be of any practical significance at the temperature of marketing and storage of the preparation.

Statistical Correlation and the Choice of Measures

There is a need in pharmacy to study the changes in structures of molecules of unknown structure. This apparently contradictory circumstance has become more evident with the advent of the antibiotic age.

In general, the primary criteria of efficacy for such compounds with such histories will be bioassays. However, bioassays as criteria of stability involve considerable expense, large error, and special isolation techniques that are frequently tedious and complex.

Prediction of stability and design of formulations may be based on studies of the rates of change of some physicochemical characteristic. Correlation of changes in the physicochemical properties with the changes in the bioassays may serve as a valid argument for the use of the former. An obvious disadvantage is that variation in the latter may not necessarily reflect in the former although the converse is not probable.

Obvious advantages are that such physicochemical studies will be easy to conduct, less expensive, can lead to prediction of the conditions that affect degradation and provide information on the properties of the intermediates and products. These facts can contribute to process design for maximum yield, the achievement of stable standards, and the least degrading assay condi-

Examples of the application of such a philosophy were the stability studies on the antibiotic fumagillin (8) (9) (10) and the antibiotic streptovaricin (5).

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A Report On Griseofulvin



R.S.C. AYTOUN*, Ph.D.,

Fig. 1. A view of some of the fermenters in the Ulverston, Lancashire factory of Glaxo Laboratories Ltd., where griseofulvin production is being carried out on a large scale.

During the past year an antibiotic effective against human skin infections of the ringworm type has been placed in the hands of the medical profession. Although this application has come to light so recently, the antibiotic in question—griseofulvin—has been known as a chemical substance for twenty years.

Early History

In 1939, A. E. Oxford, H. Raistrick and P. Simonart¹ of the London School of Hygiene and Tropical Medicine, in the course of their continuous study of the chemical substances produced by microorganisms during fermentation, published a paper describing a product of the mould *Penicillium griseo-fulvum*. They extracted and purified this chemical, which they called griseofulvin, from the fermentation broth, describing its chemistry in some detail, but made no observations on its biological activity.

Seven years later P. W. Brian, P. J. Curtis and H. G. Hemming,² at the I.C.I. Research Station at Jealott's Hill, observed that another species of Penicillium (P. janczewskii) produced a substance causing abnormal growth in certain moulds. Concentrations as low as one part in five million induced the fine threads (hyphae) of some fungi to grow in a characteristic wavy formation; to this they gave the name 'curling' and to the substance 'curling factor.' Concentrations of five parts per million caused almost complete cessation of growth, the hyphae being stunted and deformed. A year later J. F. Grove and J. C. McGowan³ proved the identity of 'curling factor' with griseofulvin previously isolated.

Further study of its biological activity revealed that it was a fungistatic substance, active against a wide range of fungi but without effect on yeasts, bacteria or actinomycetes.

The early research on griseofulvin had an agricultural bias, as at this stage it was considered likely to be a potent weapon for the control of fungal disease in crops. It was at this point that Glaxo Laboratories Ltd., who were interested in the application of antibiotics to agriculture, developed a process for its large-scale production and purification (Plate 1). Before this only laboratory scale quantities had been available to the considerable number of scientists carrying out field trials with it.

Medical Aspects

Although research on the agricultural uses of griseofulvin continues, the outlook on the antibiotic was changed in June, 1958, with the demonstration by J. C. Gentles of the University of Glasgow that ringworm in guinea pigs could be controlled by its oral administration. Confirmation of the efficacy of this method of treating guinea pigs came quickly from A. R. Marten and I. M. Lauder and J. G. O'Sullivan for calves. These three observations opened up the possibility of treating ringworm conditions in man orally.

The first published reports of successfully treating human patients by oral administration of griseofulvin came from D. I. Williams, R. H. Marten and I. Sarkany⁷ of King's College Hospital, London, H. Blank and F. J. Roth⁸ of the University of Miami and G. Riehl⁹ in Vienna. These reports have been supplemented by many others confirming the earlier results, and griseofulvin is now established in this field as an effective antibiotic.

The Nature of Griseofulvin

Griseofulvin is a colourless crystalline substance, stable under both acid and alkaline conditions and at temperatures up to those met with in the normal autoclave (120°C). Chemically it is unrelated to any of the antibiotics in normal clinical use, and it seems likely that persons who have become sensitive to other antibiotics, for example penicillin, will be able to receive treatment with griseofulvin. It is, however, sparingly soluble in water (10 to 15 parts per million). This fact may have hindered its development for agriculture, but research into its properties led to the early realisation

^{*}Glaxo Laboratories Ltd., Sefton Park, Stoke Poges, Bucks.



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Fig. 3. Photographs illustrating the progress of a case of Trichophyton rubrum infection of the finger-nail under oral griseofulvin treatment,

that the mammalian oral toxicity level of griseofulvin is among the lowest encountered in the whole range of antibiotics.

Range of Effect and Dosage

Up to the time of writing, there have been reports of effective treatment with griseofulvin both of Trichophyton infections of the hair, skin and nails and of Microsporum infections of the scalp and skin. Epidermophyton infections have also been treated successfully. In general the reported effective dosage for adults has been in the region of one to two grams per day administered orally for a period of a few weeks, the length of treatment differing with the nature of the infection. Infections caused by Candida and Blastomyces have not responded to treatment.

One of the most remarkable aspects of successful treatment is the speed with which obvious improvements in the patients' condition takes place. Long-standing infections, with a history of up to 60 years, seem to respond as readily as those of a few weeks duration. H. Blank reported a case of *Trichophyton tonsurans* of the scalp of sixty years duration that cleared in four weeks. He goes on to say that *Tinea corporis* is usually cleared in one to two weeks, the itching having ceased in three to five days and that *Tinea pedis* shows improvement in one or two weeks, but may need three or

(a) before treatment, (b) after 6 weeks aral treatment with griseofulvin, (c) after 12 weeks aral treatment with griseofulvin.

four weeks to clear completely. G. Riehl mentions a patient who had suffered from nodular mycosis of the thighs and mycotic eczema of the feet for two years. The lesions healed six days after treatment was begun.

Medical Report to Date

There have already appeared reports of something over a hundred cases treated with griseofulvin, and it is permissible cautiously to assess the results, which have been summarised by M. S. Sulzberger and R. L. Baer.¹⁰

So far, skin, nail and hair infections caused by Trichophyton Microsporum and Epidermophyton have responded to treatment (Plate III a, b & c). Improvements have often been noted within a week of beginning oral treatment. Symptoms such as itching and erythema decreased, and sweating of the infected areas, which had stopped or had been greatly reduced, gradually returned. All the investigators, without exception, agree on the effectiveness of treating these fungal infections with griseofulvin.

A careful watch has been kept on these cases for the appearance of toxic or undesirable side-effects. Severe toxic symptoms have been absent in the cases treated orally in the U.S.A. by Blank and in London by Williams, both these workers having carried out extensive examination of their patients during treatment and sub-



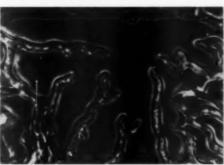




Fig. 2. Photomicrographs (x 800) showing the growth form of hyphae of Microsporum canis, one of the fungi causing ringworm infections in humans and animals, (a) growing on agar containing no griseofulvin, (b) growing on agar containing 0.3 parts per million griseofulvin and

showing the typical 'curling' form of growth, (c) growing on agar containing 5 parts per million griseofulvin showing stunted growth derived from one spere. All the above cultures have been grown for 3 days before photographing.

sequently. The former reported one case of diarrhoea and the latter mentioned that a few patients complained of thirst and one of indigestion. Other workers have reported the occurrence of headaches, which disappeared

as treatment continued.

A mention must be made, however, of a report by G. E. Paget and A. L. Walpole¹¹ of I.C.I. that very large intravenous and intraperitoneal doses (100 to 200 mg/kg body-weight and 2 g/Kg bodyweight respectively) produced evidence of mitotic arrest in rats. Oral administration has been favoured by the great majority of workers and toxicity tests have shown that far greater doses can be given by this route without toxic effects. No cases of mitotic arrest have been observed after oral therapy. In the Research Division of Glaxo Laboratories it has been found that mice could tolerate a single oral dose of 30 grams per Kilcgram body-weight, whereas the acute intravenous LD50 for mice lies between 66 and 250 mg/Kg body-weight.12

Method of Action

Griseofulvin is essentially fungistatic and not fungicidal. Its effect on the fungus is, at very low concentration, to cause a decrease in the growth rate together with the characteristic 'curling' of the hyphae. (Plate II, a.b.c.). At higher concentrations growth almost ceases and the hyphae are deformed. If the fungus even in this distorted condition is removed from the influence of the antibiotic, it will resume normal growth. Though many details of the action of the antibiotic in man and animals remain to be worked out, an outline of how it exerts its

effect can be given.

The oral ingestion of griseofulvin is followed by its appearance in the blood. Carole Bedford, K. J. Child and E. G. Tomich13 of Glaxo Laboratories Ltd., have detected the antibiotic in human serum one hour after a single dose of 0.5 g. The concentration in the blood rises rapidly, reaches a peak at 4 to 6 hours, and from then on gradually declines, though remaining detectable after 24 hours. These workers also showed that the maximum (peak) blood level reached depended on the dose. In the blood, griseofulvin is transported to all parts of the body and a proportion of the antibiotic is absorbed by those cells destined to form keratinous tissue-hair, skin and nails. These cells retain their griseofulvin content even after they have become impregnated with keratin. This absorption results in the formation of a layer of skin impregnated with the antibiotic, which is displaced outwards from the basal formative layers as skin growth continues. J. C. Gentles, M. J. Barnes and K. H. Fantes14 have extracted the antibiotic from the hair of guinea pigs fed for three weeks on griseofulvin.

Normally in infections of the ringworm type the invading fungus is actively growing in the deeper layers of the skin, and its rate of penetration roughly equals the rate of skin replacement by the basal formative layers. During treatment with griseofulvin the invading fungus meets the cells containing the antibiotic and its growth rate is greatly reduced. Under these conditions the reduced growth rate is no longer equal to that of skin replacement. The fungus is thus displaced towards the surface and is eventually removed by the normal

processes of skin erosion.

From this it will be realised that active living fungus may be present in the skin, hair or nails until all the keratin layers not containing griseofulvin are removed. and it is possible for reinfection to occur if treatment is discontinued prematurely.

G. A. G. Peterkin¹⁵ has reported that the topical application of griseofulvin in the form of an ointment is not effective as a treatment for Tinea pedis. This can be explained on the assumption that, unless topical application results in uniform penetration of the antibiotic into the deeper layers of the skin where the infecting organism is in active growth, such a method of treatment must be ineffectual.

Will Fungi Become Resistant?

One of the drawback to the use of antibiotics in the past has been the appearance of resistant forms of pathogens, necessitating higher and higher dosage rates. The question obviously arises whether the same phenomenon will occur with continued use of griseofulvin. So far many infections with human or animal pathogens have been treated, and there are as yet no substantiated reports of strains having become resistant.

Attempts to produce resistant strains of pathogenic fungi 'in vitro' have so far been unsuccessful; whereas it has been comparatively easy to produce strains of

bacteria resistant to antibacterial antibiotics.

No conclusion can be reached on this matter at the moment, though it is encouraging that resistant strains have not yet appeared.

Supplementary Forms of Treatment

Studies by many workers have clearly demonstrated the lack of therapeutic efficacy of topically applied griseofulvin. This is probably due to the great difficulty in getting griseofulvin to penetrate into the deeper layers of the skin, a phenomenon which is common to a great many other medicaments.

Indiscriminate use can lead to persons becoming sensitised to certain antibiotics, thereby rendering themselves unable to receive further treatment. It is too early to say whether griseofulvin is likely to bring about such a reaction, but until the relevant facts are known, wholesale use of griseofulvin, as of any new antibiotic, should be avoided.

The Future of Griseofulvin

Many questions on the medical use of griseofulvin remain to be answered. The full list of fungal diseases amenable to treatment with it is almost certainly incomplete. The exact mechanisms of its action on the fungi as well as in the body remain to be worked out in detail.

Knowledge of the biochemistry of the antibiotic within the body may lead to alternative methods of application involving fungi that have not yet shown any response to treatment with it. Chemists will inevitably modify the molecule, evolving new griseofulvins that may extend the range of diseases controlled. Because of the experience gained with the antibacterial antibiotics, these advances are likely to follow more quickly than they have done in the past. Human and animal diseases caused by fungi are generally not lethal, but they do cause great distress and discomfort. It is to be hoped that the era of the antifungal antibiotic has arrived.

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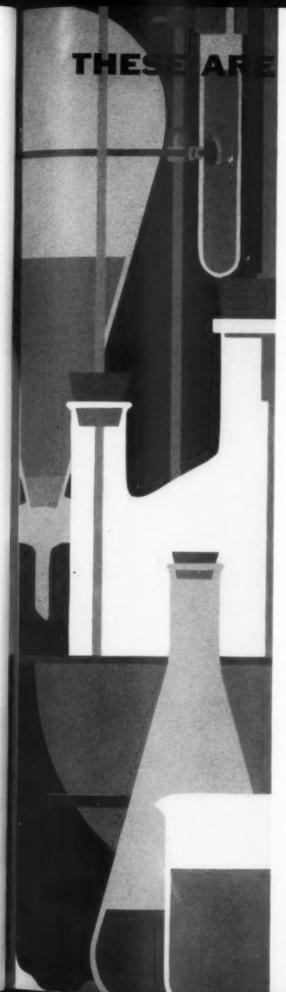
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An Evaluation Of Humectants In Cosmetic Emulsions

By GERALD C. HENNEY,* R. V. EVANSON† AND GLEN J. SPERANDIO†

An abstract of a thesis submitted to the Graduate School of Purdue University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy

A major problem associated with emulsified creams is the prevention of the drying out effect produced by evaporation of water from them. Evaporation occurs when the surface of an emulsion is excessively exposed to the atmosphere, or when the product is stored for extensive periods of time. In an effort to minimize this drying out, hygroscopic materials, or humectants, are incorporated into the creams. The polyhydric alcohols and their esters or ethers are most widely used as humectants because they are generally compatible and possess the desired physical properties.

In formulating cosmetic emulsions, consideration should be given to the desired properties of the final product when selecting a humectant. Also, the humectant used should be the one which provides optimum water retention when added in the proper quantity.

The objectives of this project were to determine the relative effectiveness of humectant materials in reducing water loss from emulsions, to determine the most effective concentration of these humectants, and to evaluate the physical properties produced by them in a simple vanishing cream.

Initial experiments were conducted to produce a cream with proper cosmetic properties. Employing a simple vanishing cream formula:

Stearic acid.																					20%
Emulsiner																					1 /0
numectants	i			٠	٠			٠	0			4		٠	0	٠	0	0	0		0-25%
Water																					54-79%

various ratios of stearic acid and emulsifier and 29 combinations of nonionic surface active agents were evaluated. A blend of four parts Tween 80 and one part Arlacel 20 was selected as the emulsifier for the formula.

Inasmuch as glycerol, sorbitol and propylene glycol are considered to be humectants of commerce, they are included in the list of materials to be evaluated. Polyethylene glycol 400 was selected to determine the relative effectiveness of a related polyol and 1,3 butylene glycol was included because claims have been made for its "mild humectancy."*

All creams were prepared in the same manner. The humectant was contained in the aqueous phase of the formula. Both phases were heated to 65°C., mixed and stirred by hand to minimize the amount of entrapped air in the finished product. The creams were placed in plastic vials having an inner diameter of 2.9 cm., an inner depth of 5.4 cm. and weighing 10.2 gm. This weight represented only a small portion of the total sample and container weight.

Table 1 — Average Per Cent Loss of Total Water Content of Creams After Thirty Days' Exposure at 10 to 20% and 60 to 70% Relative Humidity Ranges

		Per	Cent l	Humect	ant		
Humectant	0	5	10	15	20	25	
10-	-20% R	elative	Humid	ity			
Glycerol	48.4	38.6	52.9	53.1	45.3	37.6	
Sorbitol	48.4	43.1	38.6	33.3	28.5	25.6	
Propylene glycol	48.4	64.0	45.5	45.6	40.4	40.5	
Polyethylene glycol	48.4	61.7	37.5	37.5	34.5	33.8	
1,3 Butylene glycol	48.4	67.6	41.2	41.2	34.5	30.6	
60-	-70% R	elative	Humid	ity			
Glycerol	41.4	33.5	25.6	19.6	13.9	9.4	
Sorbitol	41.4	37.3	29.4	26.0	19.1	20.4	
Propylene glycol	41.4	44.6	31.6	31.1	24.0	23.4	
Polyethylene glycol	41.4	34.1	30.6	28.6	25.3	20.1	
1,3 Butylene glycol	41.4	38.5	31.5	26.4	22.8	23.0	

Samples of each cream were exposed to room temperature and humidity and to a controlled temperature of $30\,^{\circ}\mathrm{C}$. ($\pm 1\,^{\circ}$) and humidity ranges of 10 to 20 per cent and 60 to 70 per cent. A Thelco Model 4-H-2 Drying Oven was selected to maintain the temperature. A saturated solution of sodium nitrite was found by experimentation to produce a 60 to 70 per cent relative humidity range in the Thelco Oven at $30\,^{\circ}\mathrm{C}$. The samples were subjected to these conditions in the open containers. The creams were weighed before and after exposure to the test conditions and the loss in weight was accepted as the loss of water from the cream.

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The average per cent loss of total water content from four samples after thirty days' exposure at 10 to 20 per cent and 60 to 70 per cent relative humidity ranges is shown in Table 1. In the lower humidity range, glycerol was effective in 5, 20 and 25 per cent concentrations. The creams containing 10 and 15 per cent glycerol lost more water than the cream which contained no humectant. In the higher humidity range all concentrations of glycerol were effective in reducing the water loss from the creams. In the lower humidity range, a 5 per cent concentration of glycerol seemed more economical in terms of amount of water retained by the amount of humectant employed, whereas the 15 per cent concentration of glycerol was the most economical in the higher humidity range.

All concentrations of sorbitol were effective in the 10 to 20 per cent humidity range with the 15, 20 and 25 per cent concentrations being the most effective of all humectants tested in the concentrations. All concentrations of sorbitol were also effective at the higher relative humidity; however, the cream with 25 per cent sorbitol lost slightly more water than did the one with a 20 per cent concentration. The cream containing 20 per cent sorbitol showed substantial reduction in water loss at both humidities and indicates that this is the most economical concentration of humectant to be used for those relative humidity ranges.

In the lower relative humidity range, the cream containing 5 per cent propylene glycol lost more water than the cream which contained no humectant. The creams containing 10, 15, 20 and 25 per cent concentrations lost about the same amount of water. Inasmuch as the cream with the 25 per cent concentration of propylene glycol lost only about 8 per cent less water than the cream without a humectant, this material does not seem economically suitable for use in a cream which might be exposed to a 10 to 20 per cent relative humidity range; however, its use may be desired for the physical properties it produces. The 5 per cent propylene glycol was the only ineffective concentration in the higher humidity range. All other concentrations of the material were effective with the 10 per cent concentration being the best in terms of water retained for the amount of humectant employed.

The cream containing 5 per cent polyethylene glycol 400 lost more water than did the cream without a humectant; the higher concentrations of the material reduced water loss only slightly more than a 10 per cent concentration in the lower humidity range. Thus the 10 per cent concentration appears to be the most effective for that range. At 60 to 70 per cent relative humidity, all concentrations of polyethylene glycol 400 were effective in reducing water loss. Effectiveness increased as the concentration of the material was increased; however, the 5 per cent concentration seemed to be the most effective of all. Inasmuch as a 10 per cent concentration was most effective at the lower humidity range, the use of 10 per cent polyethylene glycol 400 seems justified to provide optimum protection at both humidity ranges.

Table 2 — Per Cent Water Loss from Creams Containing No Humectant

Relative Humidity, %	7 Days	Per Cent 14 Days	Loss After 21 Days	28 Days
10-20	17.7	28.9	37.0	45.9
60-70	14.7	25.0	33.5	39.4

The 5 per cent concentration of 1,3 butylene glycol was least effective of all humectants in that concentration; however, effectiveness again increased as the concentra-

tion of the material was increased. It appears that a 10 per cent concentration of butylene glycol is economically optimum at the 10 to 20 per cent relative humidity. In the higher relative humidity range, all concentrations of 1,3 butylene glycol were effective in reducing water loss although the 25 per cent concentration was slightly less

Table 3 — Average Per Cent Loss from Total Water Content of Creams Containing Selected Humectants Over a Thirty-Day Period at 10 to 20% and 60 to 70% Relative Humidities

Per Cent Humectant	7 D	ays * RWL†	14 1 %WL	Days RWL†	21 I %WL*	Days RWL†	28 %WL*	Days RWL
Glycerol					% R.H.			
5	15.4	87.0	23.6	81.7	30.7	83.0	35.5	77.3
10	20.4	115.3	32.3	111.1	42.1	113.8	50.2	109.4
15		128.8		121.1		119.7	51.1	111.3
20 25	19.1 16.0	107.9 90.4	28.9	$100.0 \\ 83.0$	31.0	103.2 83.8	43.9 36.1	95.6 78.6
Glycerol	10.0	50.4	w1.0		% R.H.		0011	
5	11.8	80.3	19.9	79.6	27.5	82.0	32.6	82.7
10	10.0	68.0	15.9	63.6	21.9	65.4	25.3	64.2
15	6.4	43.5	11.3	45.2	16.1	48.1	19.2	48.7
20 25	4.3 3.0	29.3 20.4	7.7 5.0	$\frac{30.8}{20.0}$	11.8	$35.2 \\ 24.5$	14.2 9.0	36.0 22.8
Sorbitol	0.0	20.4	0.0		% R.H.		-	
5	16.0	90.3	25.3	87.5	34.2	92.4	41.2	89.8
10	13.7	77.4	21.4	74.0	29.4	79.4	33.8	73.6
15	11.5	65.0	17.8	61.6	24.9	67.3	31.0	67.5
20	10.2	57.6	16.3	56.4	21.8	58.9 52.7	$26.9 \\ 24.2$	58.6 52.7
25 Saskital	8.9	50.3	14.6	50.5	19.5		44.4	04.1
Sorbitol 5	14.6	99.3	23.4	93.6	% R.H. 30.7	91.6	35.8	90.9
10	12.9	87.8	18.7	74.8	24.3	72.5	28.4	72.1
15	10.7	72.8	16.3	65.2	21.8	65.1	25.3	64.2
20	8.1	55.1	$\frac{12.1}{12.8}$	48.4	16.2	$\frac{48.4}{51.3}$	$\frac{18.6}{20.0}$	47.2 50.8
25 Propylene	8.4	57.2	14.0	51.2	17.2		20.0	90.0
glycol					% R.H.		01 5	1040
5 10		$150.0 \\ 111.9$	$41.1 \\ 29.7$	$142.2 \\ 102.8$	35.6 25.9	$\frac{106.3}{77.3}$	61.5 43.2	134.0 94.1
15		111.9	28.8	99.7	25.0	74.6	43.8	95.4
20	16.4	92.7	25.1	86.9	19.3	57.6	38.4	83.7
25 Propylene	17.2	97.2	26.2	90.7	19.3		39.0	85.0
glycol 5	14.1	95.9	25.5	102.0	% R.H.	106.3	49 A	107.6
10	10.8	73.5	18.6	74.4	25.9	77.3	30.9	78.4
15	9.1	61.9	16.8	67.2	25.0	74.6	30.2	76.6
20	9.3	63.3	12.7	50.8 48.4	19.3 19.3	57.6 57.6	$23.4 \\ 23.0$	59.4 58.4
25 D-1	6.2	42.2	12.1	40.4	13.0	01.0	20.0	90.4
Polyethylen glycol 400				10-200	% R.H.			
5		139.5	38.1	131.8		135.9	58.3	127.0
10	16.7	94.4	24.7	85.5	32.2	87.0	37.1	80.8
15	16.1	91.0	24.0	83.0	31.9	86.2	36.0	78.4
20 25	15.7 15.3	88.7 86.4	$\frac{22.3}{22.5}$	77.2 77.9	29.1 29.4	78.6 79.5	$32.9 \\ 32.9$	71.7
Polyethylen glycol 400	ie	0012	22.0		% R.H.			
5	13.0	88.4	21.2	84.8	28.0	83.6	33.1	84.0
10	10.6	72.1	18.4	73.6	24.8	74.0	29.9	75.9
15	9.8	66.6	16.8	67.2	23.4	69.9	27.8	70.6
20 25	8.8 7.6	59.9 51.7	$15.3 \\ 12.5$	61.2 50.0	$\frac{21.4}{17.1}$	63.9 51.0	25.3 19.9	64.2 50.5
1,3 Butylen		01.1	12.0	00.0	11.1	01.0	10.0	00.0
glycol	е			10-20	% R.H.			
5	30.1	170.1	45.1	156.1	57.2		65.2	142.0
10	17.2	97.2	25.2	87.2	32.0	86.5	36.8	80.2
15		$102.3 \\ 72.3$	26.6	$92.0 \\ 66.4$	34.8	94.1 65.9	39.4 28.1	85.8 61.2
20 25	12.8 14.1	79.7	19.2 20.3	70.2	$24.4 \\ 25.6$	69.2	29.1	63.4
1,3 Butylen					% R.H.			
5	13.0	88.4	22.5	90.0	31.2	93.1	37.4	94.9
10	11.0	74.8	18.9	75.6	25.9	77.3	30.8	78.2
15	8.9	60.5	15.8	63.2	22.2	66.3	26.0	66.0
20 25	7.4	50.3 49.7	$13.1 \\ 12.8$	52.4 51.2	19.1 19.3	57.0 57.6	$\frac{22.1}{22.7}$	56.1 57.6

effective than the 20 per cent concentration. The 10 per cent concentration was the most effective, and, since this concentration was optimum at the 10 to 20 per cent relative humidity range, 10 per cent butylene glycol should provide optimum water retention at both relative humidity ranges.

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Inasmuch as a cosmetic product will be exposed to varying humidity conditions, it is desirable to employ a humectant capable of providing optimum humectancy at different relative humidities. Sorbitol seems best qualified to fulfill this criterion; however, if a manufacturer is able to anticipate the humidity conditions to which his product will be exposed, humectant selectivity is possible.

Exposing a vanishing cream to atmospheric temperature and humidity for extensive periods of time would be an extreme condition. This situation could be closely approximated if the complete closure of a vanishing cream container was not achieved as anticipated by the manufacturer. Therefore, in an effort to reduce water evaporation to a minimum during short exposure periods, it is necessary to select a humectant which has the slowest *rate* of water loss from a specific formulation.

The rate of water loss is defined here as the per cent ratio at which a cream containing a humectant loses water per unit time in comparison with the water loss from a cream without a humectant during the same time interval.

Table 2 shows that the average per cent loss from the total water content of the creams without a humectant was about 3 per cent greater in the 10 to 20 per cent relative humidity range than at the higher humidity range after seven days' exposure; however, the difference increased to 6.5 per cent after twenty-eight days' exposure.

Table 3, showing the average per cent loss from four samples of creams containing varying types and quantities of humectants exposed to a 10 to 20 per cent and 60 to 70 per cent relative humidity range, indicates that the cream containing 5 per cent glycerol lost less water than did the cream containing higher concentrations of glycerol. The rate of water loss decreased with time in the lower humidity range; however, there was a slight increase in this rate between the fourteenth and twentyfirst days except in the 15 per cent concentration. In the higher relative humidity range, all creams containing glycerol lost less water than did the cream without a humectant. The slowing of the rate of water loss increased as the concentration of glycerol was increased; however, unlike glycerol at the lower humidity, effectiveness at slowing the rate of water loss did not increase as the exposure time was increased.

All sorbitol creams lost less water than did the cream without a humectant at the 10 to 20 per cent relative humidity range. Table 3 shows that water loss decreased as the concentration of sorbitol was increased. At the higher humidity range, the same general pattern was true except that the cream containing 25 per cent sorbitol lost slightly more water than did the cream with 20 per cent sorbitol. The slowing of the rate of water loss increased in all concentrations as the exposure time was increased.

Table 3 shows that the 5 per cent propylene glycol concentration was ineffective in the 10 to 20 per cent relative humidity range. The 10 and 15 per cent creams lost about the same amount of water; however, after twenty-eight days the 15 per cent cream had lost more water than the 10 per cent cream. The same relationship occurred in the 20 and 25 per cent propylene glycol creams. After seven days' exposure to the higher humidity range, all concentrations of propylene glycol had reduced water loss; however, after fourteen days the 5 per cent concen-

tration lost more water than the cream without a humectant. With the exception of the 20 per cent concentration, the effectiveness at reducing the rate of water loss increased as the exposure time was increased.

All concentrations of polyethylene glycol 400 were effective in reducing water loss and all concentrations increased in effectiveness at slowing the rate of water loss at the lower humidity, except the 5 per cent concentrations. The 5 per cent concentration did increase in effectiveness with time; however, it lost more water than did the cream without a humectant. All concentrations of this material were effective at the higher relative humidity range. With the exception of the creams containing 5 per cent and 25 per cent polyethylene glycol 400, the effectiveness at slowing the rate of water loss decreased as the exposure time was increased.

Table 3 shows that all concentrations of 1,3 butylene glycol, except the 5 per cent concentration were effective in the lower relative humidity range. The efficiency of butylene glycol at slowing the rate of water loss increased as the exposure time was increased, although the 15 per cent concentration showed a slight decrease between the fourteenth and twenty-first days. In the 60 to 70 per cent relative humidity range, all concentrations of butylene glycol were effective at reducing water loss. Its ability to slow the rate of water loss decreased as exposure time increased.

Visual examination of the physical properties produced by the various humectants indicated that 1,3 butylene glycol produced the hardest creams, polyethylene glycol 400 the next hardest and sorbitol, glycerol and propylene glycol produced creams of about the same consistency, which were the softest creams. Propylene glycol and butylene glycol promoted sheen development in higher concentrations almost immediately after preparation. Sheen development was negligible or undetectable in creams containing other humectants. Gloss was present in some creams and absent in others. This variety of physical properties indicates that humectant selection must not only be based on an ability to reduce water loss, but also for the physical properties that are desired in the finished product.

Summary and Conclusions

Vanishing creams were prepared containing various humectants in different concentrations and subjected to different relative humidity ranges for a thirty-day period. The effect of the humectants on the physical properties of the cream and on the rate of water release were determined.

The following conclusions are made:

1. The physical properties of sheen, gloss and consistency vary with the type of humectant and the amount of humectant employed in the formulation. Consideration must be given to the physical properties that are desired for the product when selecting the proper humectant.

2. The rate of water loss appears to be a function of the humectant used, the concentration of the material employed and the water content of the atmosphere surrounding the product; the quantity and rate of water loss from creams containing the selected humectants differ with the material used, the concentration of the humectant and the relative humidity range to which the cream sample is exposed. No humectant material from the list of selected humectants evaluated in this project was the most effective in both humidity ranges.

3. Because the efficiency of the humectant materials differs with a change in relative humidity, no one product of the group evaluated can be classed as the ideal humectant or the humectant of choice for all creams, but through selective formulation, cosmetic creams with a high degree of water retention can be developed.



Olfaction and Cholinesterase

PAUL G. I. LAUFFER*

Recent advances justify new hope of ultimate answers to two crucial questions concerning olfaction: What factors of molecular size, shape, and polarity determine how a given molecular will be attracted to the olfactory membrane? After the odorant molecule is in contact with the olfactory membrane, what happens to generate a nerve impulse?

In 1954, the writer cited (1) reasons for looking upon olfactory stimulation as simply a special case of a chemical substance affecting a nerve cell. Some characteristics of enzyme systems were reviewed, and evidence for the important role of cholinesterase in nerve transmission was touched upon. It was suggested that an odorant's ability to modify the acetylcholine-cholinesterase system was a possible key to its action on the olfactory cell. The importance of methyl groups in determining the effectiveness of cholinesterase in-

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hibitors was linked to the effect of the same groups in modifying odor intensities among the artificial musks. Steric effects, causing restricted or "geared" rotation of groups was mentioned as a possible factor in musk odor.

The Transducer

Receptor organs may be looked upon (2) as transducers whereby incoming energy of a suitable form is filtered, amplified, compressed, and encoded in a form proper for transmission to the central nervous system. We know something of the photochemical processes which initiate visual reception. There is, however, no sensory process for which we understand how the energy released by the initial mechanical, chemical, or thermal event is amplified and converted into the information carried by the nerves.

Is Olfaction a Physical or a Chemical Process?

Many students of olfaction have been much concerned with deciding whether physical or chemical phenomena are involved. In the last analysis, all must agree that the process is at least theoretically reducible to physical terms, for any chemical reaction consists of rearrangements of electrons and nuclei which follow physical laws. This fact is not altered by the terrific complexity which renders impractical the exact physical attack upon any chemical reaction involving more than two atoms.

On the other hand, one definition of a chemical compound is as follows (3): "If the electrons of a group of atoms take on a more stable configuration as the result of the grouping, the group can be considered as being combined in a compound." If this definition be accepted, there is little doubt that chemical reaction is involved in the olfactory process. Current thinking is well expressed by Dethier who says (4) that in the light of present knowledge it is highly probable that the process of olfaction and that of taste are more nearly biophysical than biochemical processes.

The chemical versus physical controversy being fruitless as well as unenlightening, let us turn our attention to recent developments which may contribute to eventual understanding of the process by which odorant molecules stimulate olfactory cells.

Vibration and Odor

Many theories, some of them rather bizarre, have attempted to correlate odor with vibrations. Some have held that molecular vibrations of certain frequencies may serve as non-sensory means of classifying odorants according to odor type. Others have held that vibrations are the actual medium of odor transmission. The foremost modern proponent of vibrations as propagators of odor is Wright, who pointed out (5) that the vibrations of frequency lower than 700 cm-1 carried enough energy for the purpose. He found (6) that 16 compounds with odors similar to that of nitrobenzene had strong lines at 150-200 cm⁻¹, and predicted, on the basis of spectra reported in the literature, that butyronitrile should have a similar odor; it was prepared, and was judged by a panel of six to have a somewhat almondlike odor. He theorized (7) that energy was transferred from the odorant to molecules of olfactory pigment by a process akin to a Fermi resonance, after surface adsorption had provided the necessary intimate contact. He suggested that the odorant molecules were then violently expelled from the cell surface by the electronic process which they had triggered in the cell membrane. In a later publication (8) Wright inclined to the view that the vibrations might either trigger the return of an electronically excited pigment molecule to its ground state, or

else increase the probability of excitation by a metabolic process.

Thompson dealt (9) rather effectively with "recent theories of smell which involve some highly imaginative views about molecular vibrations and the transfer of electromagnetic radiation." He believed that vibrations may play a part only in the same way and to the same extent as molecular vibrational energy plays a part in the mechanism of many chemical reactions, not by any radiative process. He pointed out that an enormous number of compounds have intense vibrations in the range cited by Wright for his 16 compounds with nitrobenzenelike odor, and that many of these do not have any such odor.

The idea of odor propagated from a distance by infrared vibrations was disposed of by Ottoson, who found (10) that covering the olfactory mucosa with a thin plastic film effectively prevented perception, although the film transmitted a high proportion of the energy supposed to be involved. The case for energy transfer by vibration at close quarters certainly requires more proof than has so far been adduced.

Adsorption

Many recent writers have emphasized the analogies of smell to adsorption phenomena. Moncrieff reported (11) that substances with similar odors had fairly similar patterns of behavior toward four adsorbents (activated carbon, silica gel, activated alumina, fuller's earth), and suggested that such behavior might be a means of classifying odors, and might also throw light upon the mechanism of olfaction. The same writer later cited (12, 13) data of the same nature to support the thesis that adsorption is the effective olfactory stimulus. He also performed an experiment (14) which he said (15) "showed unambiguously that the olfactory receptor region possessed powerful properties of adsorption," and which consisted of the exposure of pigmented turbinate tissue from a recently killed sheep to odorized air in a covered beaker. The air lost its odor more quickly than did other portions of similarly odorized air exposed to other tissues, although the latter also did remove the odor. The olfactory tissues also deodorized air in a jar filled with newly cut grass faster than did the other tissues. It is difficult to understand why the same results would not have been obtained if the olfactory tissue had reacted chemically with the odorants.

A later report (15) described the results of blowing odorized air into one nostril of a sheep's severed head, and out of the other, with the remaining passages sealed off. At a flow rate of 10 cc per sec., air strongly odorized with benzaldehyde came out without odor for 40 sec., after which it was odorous. With phenylacetylene the smell came through in 4 to 5 sec. These results were regarded as additional evidence for the operation of adsorption in olfaction, and 14 points were listed to support such a thesis.

Moncrieff spoke (15) of recurrent energy gains and losses at specific sites as molecules are adsorbed and released, with consequent high and low potential states. He considered adsorption a satisfactory mechanism to provide the energy needed to "trigger an enzyme mechanism, or possibly... to stimulate the nerve directly." The crucial question of the nature of the transduction mechanism was thus left unanswered, but the participation of enzymes was not ruled out in the mind of this prominent proponent of the adsorption angle.

Stoll suggested (16) that large molecules such as the amber-scented epoxides may owe their marked fatigue-producing power to strong adsorbtion on the mucosa, with low displacibility by water. Middleton reviewed

(17) the essential facts about olfaction, and concluded that they supported the thesis that odoriferous gas molecules are adsorbed on the hairs of the vesicles at the ends of the nerve fibers, and that the energy liberated by the adsorption is converted by the vesicle to an electric impulse. Ten groups of olfactory phenomena were cited as explicable on the basis of an adsorption process. The ability of formaldehyde to paralyze the perception of all types of odor was believed to point to the possibility of NH_2 and SH groups being among the active centers of the olfactory hairs.

Later, Middleton noted (18) the very low olfactory thresholds of mercaptans and aldehydes, which have a high affinity for protein and should have high heats of adsorption on protein. This situation gave some support to his concept of adsorption on the protein terminal hairs, and he suggested that the absorbed molecules might cause uncurling of the helical protein structure, with consequent disturbance of membrane permeability of the attached cells. Thus an approach from an entirely different angle led again to involvement of specific chemical groupings on the protein molecule.

If adsorption theory is to aid in solving the olfaction problem, it should facilitate the prediction of odor type or strength of given substances on the basis of their structure. Stoll suggested (19) that heteropolarity favors production of odor, and that osmophoric groups produce odor by the polarization which they generate in the molecule. In macrocyclic musks, he suspected the osmophore of performing a double function: regulating the adsorption of the molecule on the receptors, and enhancing the stimulation the molecule exerts on them. He found that odor extinction by addition of a second osmophore was in the order OH>CO>CHO>ester>epoxide>double bond, and that the same sequence was followed in the lowering of adsorption on alumina.

Davies and Taylor considered (20) that odorants must penetrate the membrane of the olfactory cell in order to cause sensation. They were able to correlate the olfactory thresholds of various odorants with their ability to accelerate the rupture of red blood cells by saponin. The same authors held (21) that olfactory thresholds depended on the adsorption energy of the odorant molecule to the olfactory membrane, and on the dislocation of the membrane caused by the adsorbed molecules. Both of these factors were evaluated numerically for some 26 odorants, and it was possible from such data to predict the olfactory thresholds of other substances.

A point of view not too divergent from that above was represented by Eyring, who suggested (22) that thinfilm chromatography seems to be involved in olfaction. Vapor chromatography, already proven so valuable in separating complex mixtures of odorants, may assist in solving problems in theory. Martin and James had predicted (23) that the difficult separation of m-and p-xylene could be accomplished on a column containing benzyldiphenyl as stationary phase. Such a separation was indeed achieved (24) by the predicted means. Later it was found (25) that a 7,8-benzoquinoline column performed the same separation more efficiently; phenanthrene, the parent hydrocarbon, behaved similarly, therefore the configuration of the stationary phase appeared to be more significant than presence or absence of the N atom. Little imagination is required to see here a convenient means of obtaining a quantitative measure of attractive forces between given odorants and stationary phases of various types, possibly leading to a useful model of the olfactory receptors. Conversely, such measurements of attractive forces may make possible the effective classification of odorants by instrumental methods.

The Nerve Cell Membrane

It is probably immaterial whether we designate the initial process of contact between odorant and cell membrane as "adsorption" or by some other name. As we have seen, some of those most thoroughly satisfied with the "adsorption" characterization have mentioned attraction to specific sites, and other significant events subsequent to the adsorption. Obviously we are dealing with an adsorbent quite different from charcoal or silica gel. It is not certain that odorants act directly on a nerve cell membrane similar to those which have been studied in other connections, but at least it will be instructive to consider some of these other studies. Bungenberg de Jong and Saubert (26) and Davies (27) had expressed the view that odor impression results from a permeability change brought about by action of odorant molecules, through van der Waals forces and hydration effects, upon cell phosphatides. Beidler considered (28) that the low free energy change (-1.22 to -1.37 gal)mole), and the small temperature dependence involved in tasting a series of sodium salts suggested a reaction such as ion binding to protein, and that the constancy of effect over a pH range of 3 to 11 denoted participation of an acidic group in the protein stronger than COOH; the phosphate or sulfate groups of nucleic acids or polysaccharides were mentioned as being qualified for participation in such a reaction.

Mullins has evolved (29) a theory of nerve cell membrane structure and function which deserves description here. He pointed out that investigation of such a membrane was handicapped by the impossibility of demonstrating a structure by optical methods, and of isolating the elements of the structure in pure form for chemical analysis. Mullins set up a model of a nerve cell membrane, assuming that it was formed not of a random polymer network, but of macromolecular cylinders arranged in regular hexagonal packing, with "pores" at the interspace of any three cylinders. Such pores were assumed to have cross-sectional diameters of the order of 4.0 A., so that they would be near to the size to fit Na+ or K+ with one hydration shell (diameters 3.67 and 4.05 A. respectively). It was assumed that an ion would pass through a pore exactly fitting its monoshell size, the hydration shells from 2 to infinity being exchanged for the hydration structure of the cylinders forming the pore. See Fig. 1.

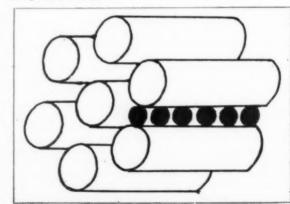


Figure 1—Model of nerve cell membrance according to Mullins, Reference 29. Interspaces between the macromolecular cylinders form peres, in one of which the black spheres represent penelrating ions or molecules. Reproduced by permission of the author and of the American Institute of Biological Sciences.

If now K⁺ ions succeed in finding a pore of 4.05 A. diameter and stream into it, thus holding it to such dimensions and distorting at least the 12 surrounding

pores, some of the pores will be properly sized to fit the which he reported (32) as arising from Brownian Na+ ions which have been waiting for an opportunity to penetrate the membrane. Na+ will stream through,

thus creating a nerve impulse.

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Mullins showed how various data on narcotic potencies of hydrocarbons could be explained by the above model. For instance, toluene has a narcotic threshold for grain weevils four times as high as that of benzene; such a difference would be expected from the ease with which a symmetrical molecule such as benzene would enter the pores and block ion travel, and the lesser ease with which toluene could enter, due to its projecting methyl group.

It has been conventional to postulate the existence of special receptors on the nerve cell surface to accommodate excitatory substances, but for these also Mullins found his model to provide a plausible explanation. He considered it likely that the filling of a membrane pore with molecules that fit closely would initiate the same transitory increase in Na+ influx as that produced by K+. Irregularly shaped molecules introduce, of course, many complexities, especially if they have strong polar groupings. The orientation of such a molecule in a membrane interspace, and the strength of its binding to specific points within the interspace would undoubtedly be factors to be considered.

Cholinesterase and the Cell Membrane

Mullins proceeded (29) to consider how his model might serve in interpreting known data on participation of the acetylcholine-cholinesterase system in nerve conduction. The flexibility of the acetylcholine molecule introduces complexities, and we do not know whether the cholinesterase is just outside the cell wall, just inside the cell wall, or in the cell walls as part of a mosaic containing both cholinesterase and a receptor for acetylcholine.

It has been suggested that cholinesterase and the acetylcholine receptor are identical, but Mullins' data indicate rather that enzyme and receptor both are aspects of the activity to be expected from a membrane such as that described above. Cholinesterase inhibitors would act by decreasing mean interspace diameter, shutting off access of acetylcholine to the enzyme without occupying every active site. Thus ethyl chloracetate, which lacks the two points of attachment generally required for complex formation, nevertheless shows substrate inhibition; the tertiary analog of acetylcholine, diethylaminoethyl acetate, which binds almost as well as acetylcholine and has two points of attachment, does not inhibit; therefore either the quaternary structure or the chlorine atom appears to be capable of distorting the interspace distribution because of nonconforming shape, while the tertiary structure provides a better fit. In eserine the center of positive charge and the CO group are 1.1 to 1.4 A. farther apart than in acetylcholine fully extended, therefore eserine is assumed to fit pores larger than the mean, acetylcholine to fit pores smaller than the mean.

Mullins' model represents a simplification of a highly complex system. Folch-Pi pointed out (30) that in tissues most structural proteins and lipids are tied into lipo-proteins, and that wherever there is a hydrophobic lipid area, there is a hydrophilic protein layer nearby. Also, that a membrane is not a mechanical thing which does not change; it can be expected to change its structure from one physiological condition to another. Ling remarked (31) that penetration of a membrane by a charged particle, as indicated by isotope studies, seems to depend on alternate association and disassociation with charges on the pore surface. Such a process may have a connection with Kirkwood's "fluctuation force"

movements of the mobile protons when two protein molecules in fixed orientation are separated by a small distance, and which would cause each molecule to produce an alternating electrical field at the point of location of its neighbor.

Biological Specificity

Kirkwood remarked (32) that considerations relative to the specificity of the "fluctuating force" must remain speculative until more detailed knowledge of the fine structure of proteins is available. There are however some more familiar cases of specificity which might by analogy shed light upon the molecular features responsible for creating the specific olfactory signals involved in recognition of odor. Pressman observed (33) that in many cases of biological specificity there seems to be a close complementariness of fit of active site of receptor molecule about its substrate, so that enough weak, shortrange forces can come into play to hold the molecules together. When antibodies are formed against a hapten, they act as though formed against the van der Waals outline of the hapten as template. Haptens of similar van der Waals outlines react with antibodies with efficiencies lessening as their similarity decreases. It is not necessary to have a charged group to obtain specificity toward haptens. The hydrated configurations of various ions were regarded as the determining factors in many cases of molecular specificity.

Yos, Bade, and Jehle considered (34) the conditions under which the London-van der Waals dispersion forces between two particles immersed in a medium would constitute a specific attraction. The physical-chemical data for correct evaluation of such forces in macromolecules are not yet available, but molecules are considered to be identical with respect to London forces if they have the same distribution of polarizabilities

Hirschfelder described (35) the mutual polarization that occurs as two molecules approach each other, the charge distributions becoming readjusted so as to make the energy of the two-molecular system as low as possible. In conjugate double bond systems, and in many other molecules concerned in biological reactions, very little effort is required to make large changes in electric charge distribution. Polarization forces are therefore very important here; resonance forces are probably of

little importance in explaining specificity.

Pauling characterized (36) the forces between molecules of antigen and those of antibody as undoubtedly weak intermolecular forces that individually are nonspecific, but that become specific because of the spatial relationship of the different parts of the combining region of the antibody in relation to the surface structure of the antigen. Fit of antibody around antigen is within 1 A., and serious steric hindrance follows replacement of hydrogen in the hapten by methyl. When H replaces CH3, the loss of binding energy is about 1 kcal./mole, a reasonable amount to interpret as resulting from van der Waals attraction of the surrounding atoms for H, as compared to that for CH3.

Kirkwood emphasized (37) the importance of considering the mutual attraction of water molecules in problems of biological attraction. In aqueous solution the direct interaction between two methyl groups is virtually negligible in bringing them together, compared with the energy gained by making more contacts between the water molecules previously surrounding the methyls. A similar interaction is responsible for formation of soap micelles, the hydrocarbon portions being crowded together by the water, but the COOH or SO3H groups forming a protective layer which interacts with the water and prevents separation into two phases. In protein structure, stability due to direct H bond formation is reinforced by the effect of water in squeezing the chains into contact.

Klotz and his coworkers showed (38) that metal ions such as Hg++, Cu++, Ag++, Ni++, Co++, Mn++, and Zn++ were effective mediators in causing strong complex formation between proteins and small molecules not ordinarily bound, such as azopyridines. They concluded (39) from thermodynamic data that all portions of the small molecule contribute to the net binding effect, and that binding involves not only protein sidechains but other portions as well; the distance between positive and negative groups of the small molecule determined the method of binding in some instances. They found that the dimethylamino group of an azo dye bound by its mecuriaceto group to the SH of serum albumin formed salts ionized to a much smaller extent than the salts of the same dye similarly bound to cysteine, and explained this (40) on the basis of the shell of water of hydration which surrounds the protein with a more or less rigid "iceberg," hampering the movement of ions.

Enzymes

The dean of odor chemists, Ruzicka, recently expressed the opinion (41) that the data obtained by research in the field of odor and structure fit very well into the broader picture of relationship between physiological properties and chemical structure. The study of enzyme systems has shed so much light on the latter field of inquiry, that we shall be well advised to bring such concepts to bear upon the problems of olfaction.

There have been many recent additions to the circumstantial evidence implicating enzymes in smell. Beer and Quastel reported (42) that acetaldehyde and valeric aldehyde inhibited potassium-stimulated respiration by their effect upon a step in the citric acid cycle; also (43) that the C-2 to C-5 normal alcohols inhibited brain-cortex respiration by affecting the brain-cell membranes. Absorbable Se compounds both inhibited dehydrogenase (44) and caused anosmia, presumably by blocking SH groups.

Certain reported alterations of olfactory function at least suggest enzyme participation. Le Magnen and Rapaport noted that rats with severe vitamin A deficiency could not make odor discriminations which were normally possible (45). Goetzl found (46) that Angostura bitters and tannic acid ingested with meals prevented the decrease in olfactory acuity generally noted after a heavy meal. Stoll reported (16) a difference in the quality of sensation produced by musk and civet odors in men and in women: men found them pleasant; women found them to produce pleasure, even joy, but only when smelled in great dilution.

Meanwhile, there has been considerable progress toward penetrating the tangled jungle of enzyme mechanisms. Five years ago the concept of acidic and basic centers, spaced at a critical distance within the enzyme structure and cooperating to produce its catalytic effect, was new. Koshland has evaluated (47) the various factors which have been considered to be possible operators in engineering the enormous multiplication of reaction rates (10⁷ to 10¹¹ times) characteristic of many enzymes. He demonstrated that the factor of acid-base catalysis, or catalytic group orientation, was the only one with anywhere near the necessary degree of potency.

Koshland and Erwin found (48) that phosphoglucomutase contained the same active site sequence (aspartic acid: serine: glycine: glutamic acid: alanine: valine) as had been found in chymotrypsin. Thus an enzyme which transfers phosphate between carbohydrate molecules, and one which hydrolyzes peptide bonds

have active sites with at least this much in common. They considered that this sequence about serine is involved in making the otherwise inert $\mathrm{CH}_2\mathrm{OH}$ side chain reactive. The amino acids determining specificity were believed to be more remote from serine, perhaps in adjacent coils.

Cholinesterase

In an earlier contribution, the writer proposed (1) that consideration of an odorant's ability to affect the acetylcholine-cholinesterase system should be a fruitful approach to the study of its olfactory effect. Dettbarn, Wilson, and Nachmansohn have reviewed (49) recent evidence for the participation of acetylcholine in propagation of the bioelectric currents which constitute the nerve impulse. Del Castillo and Katz showed (50) that the drug acceptors and the acetylcholine acceptors in the motor end-plate are identical. Zupancic considered (51) that many biologically active substances produce their specific effect by reaction with the enzyme which inactivates them, citing the inhibiting effect on cholinesterase of certain quaternary ammonium antagonists of tubocurarine. Application of acetylcholine increased (52) the sensitivity of human taste receptors.

Fisher found (53) that the relative affinity of various drugs for wool was a useful measure of their effectiveness in various actions on drug cells. He considered the wool protein to be acting as an enzyme model, and more specifically as a model for cholinesterase. Adsorption of compounds on wool may simulate the combination of the cationic head with the anionic sites of the cholinesterase receptor. When cholinesterase is built into a membrane, the latter becomes a "permselective" membrane. Adsorption of quaternary ammonium compounds appears to interfere with normal cholinesterase function either by neutralizing the anionic groups necessary for enzyme action, or by a steric interference preventing enzyme action by covering too much surface.

In summarizing the factors determining specificity in reactions involving cholinesterase, Wilson noted (54) that the closest possible approach of a quaternary methylated ammonium ion (r = about 3.5 A.) to a negative group is about 5 A., and that it is rather well established that there are ionic forces of attraction between substrate and enzyme which play an important role in binding and catalysis. The methyl groups of the cationic head probably are also attracted to hydrocarbon portions of the protein by van der Waals forces. The COO—group, existing as a resonance structure, is looking for electrons and may form a weak covalent bond with a basic group in the active site of the enzyme. Thus two subsites are recognized in cholinesterase.

The strategic importance of the methyl groups in the acetylcholine-cholinesterase system is of possible value in explaining the similar effectiveness of methyl groups in determining odor type and strength in many series, notably the musk odorants.

Steric Considerations

Each year it becomes clearer that the three-dimensional structure of the odorant molecule must be considered in all its aspects in order to establish odor-structure relationships. Recent advances (55) in the understanding of steric effects have greatly enhanced the effectiveness of this approach. The vapor chromatograph and improved spectrographic methods have helped to remove some of the stumbling blocks caused by reports of odor types and intensities which were erroneous due to impure samples. Thus earlier writers had cited the "powerful petrol smell" of n-octane as evidence against chemical activity operating in olfaction, but Mullins recently reported (56) that pure n-octane has

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a very weak odor, the petrol odor of impure samples being introduced by cyclic hydrocarbons removable from commercial octane only with great difficulty.

Earlier reports had cited many odor differences between enantiomeric compounds, but recent opinion inclines (57) toward the view that pure enantiomers have identical or similar odors. Naves in reviewing odors (58) of stereoisomers noted that no case is known where one enantiomer is odorous, the other not. He characterized odors of ethylenic (cis-trans) stereoisomers as clearly distinguishable, and those of cyclanic stereoisomers as having marked differences. Naves expressed the opinion that any progress in the knowledge of the olfactory mechanism is likely to stem from new research on the stereochemical factors of odor. Thompson also predicted (9) that a satisfactory understanding of smell will probably be based upon knowledge of the detailed molecular and spatial configurations of olfactory pigments and organs, and of the odorant molecules them-

The most elusive factor in the steric designation of molecular shape is no doubt that of conformational structure, or the relative positions assumed by the groups attached to two carbon atoms which are joined by a single bond. In ethane, the eclipsed conformation (in which each hydrogen on the far carbon would be hidden by a hydrogen on the near carbon, as one sighted along the C-C axis) has an energy about 3 kcal. higher than that of the staggered conformation. Bulky groups can hinder rotation about a single bond to such an extent as to preclude it. Pauling recently remarked (59) that 18 years after the discovery of restricted rotation around single bonds there is still no valid theory to cover it, and Pitzer noted (60) that his attempts at calculations of the quantum mechanical basis of these potential barriers had so far been unsatisfactory.

Mullins concluded (56) that "rigid molecules with certain shapes are very much more effective olfactory stimulants than are flexible molecules," suggesting that odorants excite by producing a local disorder in the oriented molecules of the cell membrane. His poresizing theory of nerve stimulation has been described above. He cited the butanes, butenes, and butadienes to illustrate how certain rigid shapes went with high odor intensity, for cis-butene-2 had about 100 times the intensity of trans-butene-2 or of n-butane.

Differences in odors of cyclanic stereoisomers may well be correlated with the differences in chemical activity which are well recognized (61), the axial substituents being in general more crowded and more subject to steric hindrance than the equatorial ones. Oki concluded (62) that among homologs of stilbestrol, strength of estrogenic activity could be correlated with the degree of rotation of the benzene nuclei, or with the consequent molecular thickness, produced by the steric effects of the alkyl substituents.

Beets and Witjens had shown (63) that the spectra of β -iso-methyl-ionone, as well as calculations from models, indicated steric hindrance preventing coplanarity of carbons in the unsaturated sidechain with those in the β -cyclic double bond.

Musk Odorants

Beets more recently noted (64) that most modern odor theories share the concept that the odor of a molecule is determined by two separate contributions, one from the form and bulk of the molecule, the other from its functional group or groups. If tendency to form H bonds determines at least partly the olfactory efficiency of the functional group, then tert-butyl, methyl and halogen can only be profile groups, but CHO, COCH3, and CN are more or less functional groups.

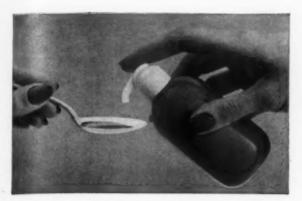
In nitro musks, Beets considered that the nitro group must be able to act as either functional or profile group, and to play the part either of a tert-butyl or of a CHO, COCH₃, or CN group. Among benzene derivatives, the minimum requirements for musk odor appear to be two quaternary carbons and a CO group, di-tert-butyl-benzaldehyde being the simplest molecule with musk odor reported. A molecular weight of 200 to 300, a closely packed, compact structure, and a functional group seem to be general requirements for musk odor in benzene, indane, or macrocyclic series.

Figure 2.—Compounds A, B, and C, each containing a hindered nitro group whic is ferced out of coplanarity with the benzene, have musk ader. Compound D whose CHO group can fit in a caplanar conformation, has no musk eder.

In Figure 2, compound A, the unhindered nitro can be replaced by either CHO or tert-butyl, giving compounds B and C, without destroying the musk odor, but replacement of the *hindered* nitro of C by CHO, which is coplanar to the ring, to give compound D, removes the musk odor. Therefore the out of plane nitro, with its thickening effect, its small solvation tendency, and its inhibited resonance, must contribute to the musk odor. Beets remarked that in benzene musks with only one functional group, CO is the only one very efficient.

functional group, CO is the only one very efficient. Naves also concluded (58) that appearance of musk odor correlates with the resonance hindrance expressed in the U-V absorption spectra. The infrared bands at about 1380 cm $^{-1}$, related to the symmetrical vibration of the nitro group, are shifted (65) by introducing o-alkyl groups. In systems containing the acetophenone unit, the values of $\lambda_{\rm max}$ for U-V absorption were found (66) to remain essentially constant while those of the extinction coefficient decreased, as the phenyl and CO groups were forced from a coplanar configuration by steric factors, suggesting that only those molecules whose CO and phenyl were nearly coplanar could undergo excitation.

The list of musk odorants continues to grow (64) and these compounds, sprawling over six categories considered quite different by orthodox methods of classification, offer a unique challenge to anyone interested in the structure-odor enigma. Somewhere in these seemingly diverse structures there must exist similarities which, if recognized, should sharply advance our ideas of what produces odor. A start was made years ago when Prelog and Ruzicka noted (67) that the first steroid musk discovered by them, Δ^{16} -androsten-3-a-ol, had a structure similar to one conformation which could be conceived for the macrocyclic musk civettone. A conformational link between benzene musks and indane musks is suggested by the easy transition from one series to the other, which has occasionally caused incorrect structures to be assigned. Thus the product of reaction of p-cymene, tert-butyl alcohol, and sulfuric acid, formerly thought to be 1-methyl-3-tert-butyl-4-isopropyl-benzene was recently shown (68) to be 1,1,3,3,5-pentamethylindane. The transformation was ascribed to removal of a-H from the siopropyl group of cymene by the tert-



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Olfaction and Cholinesterase

Circumstantial evidence has been cited above linking olfaction to enzymatic processes. The usefulness of the acetyl-choline-cholinesterase system (53) in explaining the activities of chemical substances in producing effects on other nerve cells recommends its consideration as a model for olfactory processes. The role of acetylcholine in propagation of nerve impulses (49, 50, 51) strengthens the recommendation. The concept (64) that the form and bulk of a molecule combine with a strategically placed functional group to condition odor fits in well with the known factors influencing inhibition of cholinesterase. More specifically, methyl, isopropyl, and tert-butyl groups exert a dominant influence in the bulk factor, CO groups as the functional group, among the musk odorants and also among the cholinesterase inhibitors.

It is therefore clear that comparison of the extensive data at hand on musk odorants, with the principles derived from the study of cholinesterase inhibitors, should shed much new light upon the odor-structure puzzle. Whether odorants are thought of as acting to inhibit cholinesterase in the olfactory cells, and thus to influence the nerve impulse; or whether they are thought of as acting by "adsorption" on a surface analogous to cholinesterase, and generating electrical energy by uncoiling or denaturing the protein (17, 69, 70); the work already done on cholinesterase will yield valuable clues as to the structural features most likely to be significant.

Summary

In the past five years new data and concepts have brought closer the ultimate understanding of olfactory mechanisms. Promising keys include:

The gross analogy of initial "adsorption" of odorants on the olfactory membrane to their adsorption on inorganic surfaces.

-The correlation of olfactory thresholds with adsorption energy.

3-Chromatographic data as means of devising true models of the olfactory receptors, and as means of classifying odorants.

-The possible "denaturation" or uncoiling of the olfactory cell protein by adsorbed molecules, with conse-

quent release of an electrical impulse. 5-The concept that odor sensation may result from a permeability change caused by action of odorous molecules, through van der Waals forces and hydration ef-

fects, upon cell phosphatides. 6-The concept that odorant molecules may distort nerve membrane pores so as to allow Na+ to enter the cell and generate an impulse.

7-The use of van der Waals outlines of molecules to determine closeness of fit with receptors.

-Heteropolarity as a determining factor in odor production, with osmophoric groups producing such a condition in the odorant molecule.

9-Distribution of polarizibilities within a molecure as a determinant of specific attraction.

10-The characterization of biological specificity as the result of spatial distribution of weak attractive forces which, taken singly, are nonspecific.

11-The importance of water of hydration in determining the effective size and shape of biological molecules, in hampering the movement of ions, and in influencing attractive forces.

12-The determination of the amino-acid sequence of the active sites of several enzymes, and the separation of catalytic site from specific site.

13-The discovery that suitability of a compound to inhibit cholinesterase is correlated with its adsorbability on wool protein, and with its effectiveness in several types of action on nerve cells.

14-The increased understanding of steric effects, and advances in determination of conformational details of structure.

15-The determination of strategic groupings and distances for inhibition of cholinesterase, which should be directly applicable in interpreting the effects of similar factors in olfaction.

Conclusion

Recent advances justify new hope of ultimate answers to two crucial questions concerning olfaction:

-What factors of molecular size, shape, and polarity determine how a given molecule will be attracted to the olfactory membrane?

2-After the odorant molecule is in contact with the olfactory membrane, what happens to generate a nerve impulse?

May we hope that olfaction will be the first sense for which the nature of the transducer will be elucidated?

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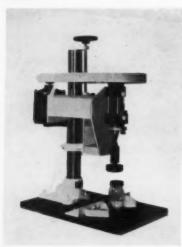
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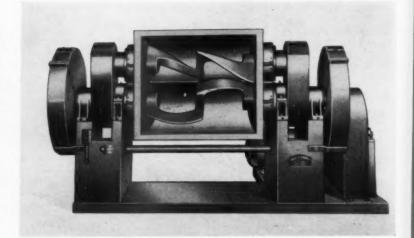
PASTE MIXERS-1

A new line of paste mixers which embody several improvements in design and construction which assure long service under severe operating conditions, freedom from contamination, and a minimum of maintenance and lubrication have been announced. These new mixers have double rows of lubricated bearings, located to give the shafts maximum effective support for complete rigidity. These bearings are of the extremely lowfriction type and can be used at elevated temperatures, if necessary, the manufacturer asserts. Improved seals assure freedom from contamination. Precisionbored housings for the bearings and seals provide accurate alignment which is built-in for the life of the mixer. The seals are easily accessible for maintenance.



2. SCREW CAPPER—2

A new type of air operated screw capper, suitable for all sizes of lug and screw caps, molded and metallic, on glass, tin and plastic containers has been announced. Uniform cap tightening is secured via an adjustable friction clutch which can provide any closing torque required for all sizes of caps. This eliminates "breathers" and prevents spoilage as well as loss thru evaporation. Quick-change chucks provide for immediate change-overs from one size or type of cap to another. Up to 50 capped containers per minute can be readily secured without operator fatigue, a spokesman for the manufacturer states.



1.

GLASS PIPE

The availability of a wide line of Kimax tempered industrial glass pipe and fittings was announced by Kimble Glass Company. Manufactured from KG-33 borosilicate glass, the new pipe and fittings match or excel the performance of any similar line now being produced.

The entire line of pipe and fittings is sold and distributed nationally by the Glass Products Division of the Fischer & Porter Company, Hatboro, Pennsylvania, manufacturers of process instrumentation and industrial glass products.

Kimax tempered pipe has a wide application in many industries, including pharmaceutical and chemical according to the manufacturer. It possesses corrosion, chemical and heat resistance, clear-view transparency and ruggedness. Tests have shown that KG-33 glass is resistant to all types of solutions with a few exceptions, such as hydrofluoric acid.

ANALYZER

A new analysis system for continuous automatic analysis of chromatographic fractions was announced in July. Called "AutoAnalyzer, and operating as a separate analytic entity in the chromatographic set-up, the system can accurately handle either the full-stream delivery of the column effluent or any part thereof. Up to 60 samples per hour can be handled by this self-cleansing system which

is applicable to such diverse materials as amino acids, proteins, peptides, polypeptides, steroids, phosphates, and many others, according to the manufacturer.



3.

COLONY COUNTER-3

Bacterial colonies can now be counted and marked simultaneously in a single probing action.

The illuminated electronic colony counter records pathogenic and non-pathogenic colonies with great accuracy and provides the operator with four different electric counting devices. An electronic marking probe, electric marking pen, fixed pushbutton counter and a remote, hand-seld pushbutton counter.

On contact with any agar medium the sensitive Marking Probe actuates a counting mechanism as it makes an identifying puncture in the colony.

for the manufacturer states. dled by this self-cleansing system which ing puncture in the co

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Possibilities of Standardisation in the Aerosol Industry

by Dipl. Ing. Tangermann (Germany)

An Abstract

Conditions in the Aerosol Industry are varied. A wide variety of products are offered, to which new ones are continually added. The circle of suppliers is widespread and increases continuously. Between the various companies there is lively competition. Customers have the most varied interests resulting from the fact that they live in five different continents of the world with their different climatic conditions and habits of life. Regulations for standardisation cannot be expected for such a wide range. The basis for setting up and maintaining standards is completely dependent on the good will of those concerned. It presupposes a high degree of community sense. The basis for effective standardisation in the aerosol industry is therefore very narrow, but nevertheless an attempt should be made at a beginning. Such a beginning will doubtless entail certain difficulties which can only be overcome where on the one hand, considerable advantages are obtained, and on the other hand, where there are common interests which make it possible. This leads to the decisive question-what are the advantages of standardisation overall? A general consideration shows the wide range of problems touched by this subject. If treated exhaustively, the possibilities of standardisation in the following fields would have to be discussed in detail: (a) the contents; (b) the packaging; (c) the equipment. This cannot be done entirely within the framework of this paper. Already because of time limitations a number of points will have to be confined to a specific survey. A few special points, however, will be discussed in detail, namely those for which at the present stage positive suggestions for standardisation can be submitted. Standardisation of

Packaging: The consumer is offered a very wide range of containers. There are different kinds of packages, a variety of sizes and a multitude of dimensions and shapes. The aim of standardisation is to simplify the market to a certain extent, by limiting the hitherto large assortment to a few types which can be economically produced and filled, which simplifies stock-keeping and trading and which limits profiteering so that the

consumer can be provided with suitable packages under favourable conditions. Types of Container: At the moment packages of four basically differing types are offered which differ by the material from which the container is made. In addition to tin plate cans an increasing number of aluminum containers are now used, as well as glass bottles with or without plastic cover, and bottles made only of plastic. Each of these types of packaging has found a certain field of application according to the properties of the material. Due to the numerous requirements resulting from the characteristics of the materials with which they are filled and from the demands of the consumer, the applications of the various types of packaging overlap to a great extent. Theoretically one could envisage at least limiting this overlapping by standards. It is however hardly to be expected that such a limitation could be achieved by voluntary agreement. The idea of simplifying the market by limiting the applications for certain types of packages does not therefore offer practical possibilities at the moment. Sizes of Packages: Aerosol containers are supplied in numerous different sizes. A systematic grading of the actual size of contents does not exist.

The differences between adjacent sizes are so small that no practical importance can be attached to them. The great variety of sizes of packages makes the market difficult and impairs the economy. Reasonable standardisation would result in a number of advantages to manufacturer, dealer, and consumer. Recognizing this fact, the proposition was made that a series of standards should be created for the sizes of aerosol packages, which would consist of a total of four different sizes.

It would be desirable if this series of standards were accepted on as wide an international basis as possible so that the advantages to be obtained by this standardisation would be realized not only in the individual countries, but international trade also, for instance, within the European Common Market would be simplified, as has already been successfully accomplished with canned food.



Atlas Certified Colors

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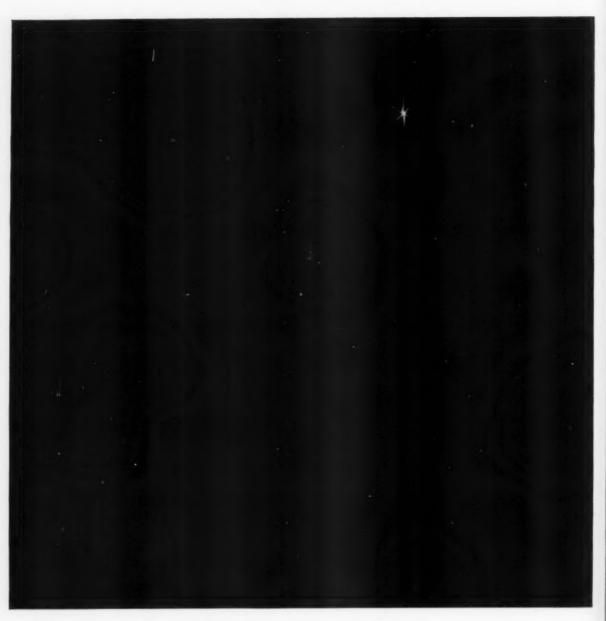
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CHEMICAL PROBLEMS CONCERNING THE PERFUMING OF AEROSOLS

by Dr. P. H. Witjens Research Department, Polak & Schwarz, International N.V., Hilversum, Holland

An Abstract

The research work mentioned in aerosol literature deals mostly with the physical properties of the propellants and the other components of the aerosol. However the rather slight chemical reactivity of the propellant does play a big part in problems of aerosol in that it effects the stability of the pressurized product. Illustration of a single aspect of this in greater detail shows one of the ways in which a change of aerosol and especially of the odour developes. A change of odours can give the first indications that the container's contents are not completely stable. Experiments were carried out using a system serving as a prototype of a group of aerosols with a substantially cosmetic application, based on:

Propellants, Oxygen, Water, Ethyl Alcohol, and Container Material. The propellant used for products of this group is usually a mixture of difluoro-dichloromethane and monofluoro-trichloromethane. The most important purpose of the latter is to reduce the pressure of the mixture to such an extent that it falls below the value considered safe for commercially available tin plate aluminum containers. All the components are brought into contact with each other, care being taken that the liquid phase is homogeneous. The mixture is then stored under two different sets of conditions, one at 100° for seven hours, the other at 55° for 14 days. Apart from a lowering of the pH of the mixture which could be expected under such conditions, the presence of acetaldehyde and acetaldehyde diethyl acetal could also be demonstrated. As the quantities of these reaction products formed were very small, their presence in the reaction mixture was determined by gas chromatography analysis. An attempt, based on these results, is being made to define the conditions under which these products are being formed. From the observations mentioned the following hypothesis on the reaction-pattern can be deduced: Under the influence of acid, formed from water and fluoro-trichloro-methane, and metal or metal halide, the ethyl alcohol is being dehydrogenated to acetaldehyde and this in turn is partially converted into the corresponding diacetal. The atmospheric oxygen can be primarily considered as the hydrogen acceptor.

In the presence of tin plate, atmospheric oxygen promotes the formation of acid as well as acetaldehyde but its absence does not however exclude the processes completely. The substantially complete absence of moisture depresses the formation of aldehyde almost entirely although some acid is still being formed. If the products in question are perfumed, it is clear that a lot of other condensation, esterification, reesterification and acetalisation reactions can take place, by which the character of the perfume composition can be radically changed. All these processes can take place before corrosion actually occurs and before the aerosol is unsaleable for that reason. In conclusion: in the formulation and filling of monofluoro-trichloro-methane containing aerosol, the presence of products which can act as a hydrogen acceptor must be excluded as much as possible. As far as pressure filling is concerned this means that it is recommended that the air present in the container be removed or replaced by an inert gas.

Methods of Determination of the Granulometric Characteristics of Aerosol Sprays

Mr. Pette, Ing. Chim. I.C.N. (France)

An Abstract

Whatever the definition that is adopted for aerosols, it is always the dimensions of the dispersed particles in these systems that characterise them. This is logical since variations in the properties of an aerosol are continuous frunctions of these particle dimentions. The true aerosol-defined as a colloidal dissemination of a liquid or a solid in air-was arbitrarily limited to the dimensions of particles between 0.1 micron and 1 milimicron—this region being between 10-5 and 10-7 cm. and which is in fact characteristic of the dimensions of colloidal particles. It is difficult to find a precise demarcation line between the different states of matter, and even though aerosols of our low-pressure bombs do not possess the characteristics mentioned above they still retain the name. The expert committee of the CMS (O.M.S. no. 54 Comite d'experts des insecticides Geneve 1952, p. 32) has adopted the following distinguishing characteristics for insecticidal aerosols:

Dimensions of particles mean diameter in μ

Atomisation in la	rge drops	400	and more
Atomisation in fin	e drops	100	to 400
Mists		50	to 100
Aerosols		0.3	5 to 50

The result is that this definition is just above the limit of collocidal material and consequently within the hazy region of properties that pertain to both colloids and suspensoids. Many examples prove that the properties of aerosols are functions of the dimensions of the particles. Studies on silicosis lead us to consider as dangerous fine particles of a diameter less than a few microns—the figure normally accepted being 3 μ with maximum alveolar retention in the region of 1.0 μ .

The obscuring power of a smoke generating screen

is most efficient for particles in the order of 0.5 microns.

The efficacy of an insecticide is so manifestly under this domination that certain American Research Scientists (V.K. La Mer & S. Hochberg Chem. Rev. 44 no. 2, 1949, p. 341) have given-for a certain type of insect -a definite mathematical relationship connecting the concentration of the toxic agent, the diameter of the particles, and the time required to kill 50% of the female mosquitoes tested. Innumerable examples could be quoted but one fact remains both the good and bad effects of aerosol must be attributed to the distribution of their granulation and to the dimensions of their particles. Good effect, justified by the increasing success of low-pressure preparations; bad effects-if we take into account the loud and insiduous disasters that they cause in the world. Dust explosions and pollution of the atmosphere, needless to say, are permanent dangers that place the price of an era of industrial progress upon the shoulders of a certain class of worker in particular, and upon all of us in general. We propose in this study to measure the dispersion of our low-pressure aerosols by a simplified but nevertheless accurate method which like all others is based upon the determination-by means of the optical microscope-of the average diameter of a mass of particles collected on a special base. In all measurements of this kind the problem comprises three phases: (1) Selection of the samples; (2) Measurement of the different particles of the sample; and (3) Expression of results. Each one of these phases has been the object of such study for the problem of aerosols and has been attracting the attention of the scientific world for a very long time.

Thus in our particular case—low pressure aerosols there results a simplification which consists in chosing those methods in fine dispersion experimental technique which lead up to the required results.

Trade

Literature

The following booklets have come to the attention of the staff of *American Perfumer & Aromatics*. They are available to readers from the sources mentioned. *Editor*.

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An illustrated booklet, describing its expanded activities in the aerosol fieldmanufacture and development of valves and complete dispensers-has just been published by the Aerosol Division of The Risdon Manufacturing Company, Naugatuck, Conn. The comprehensive, 16-page 81/2" by 11" booklet is printed with a full-color cover, and in three colors throughout. Described in detail are each of the firm's valves, including the 5210 (for metal containers), the GB (for glass, plastic and small containers), the Micro-Mist for three-phase products or ultra-fine spray, the metered spray and the Magna-Meter for liquefied or compressed gas propellants. The booklet also describes the variety of stock or custommade actuators and protective caps that Risdon offers.

Sulfur

A chemical safety data sheet on sulfur has been published by the Manufacturing Chemists' Association.

The 15-page booklet gives step-by-step instructions for unloading molten sulfur from tank cars. It covers "dome" unloading by air pressure and "bottom" unloading by gravity flow, pump or air pressure. Other sections of the booklet cover the physical properties of sulfur, engineering control, employee safety, protective equipment, fire fighting, handling, storage, tank cleaning, medical management and first aid.

Valves

Specifications for three types of aerosol valves are listed in a new bulletin prepared by Valve Corporation of America. The valves are VCA's B-9 for use in standard one-inch opening containers, the B-18 metered valve for glass bottles or one-inch opening containers, and the B-8 valve for glass bottles. Data includes sizes and materials in which valve components are available.

Esters

'Metholene Esters for Alkylolamides is the title of a new technical bulletin offered by Emery Industries. The procedure is given for using methyl esters of fatty acids as intermediates to produce "super" grade amides having active amide contents of more than 90%, compared to the less than 70% obtained by direct amidation of free fatty acids. Also listed are complete specifications for Emery's Metholene line of methyl esters, including methyl stearate, palmitate, myristate, laurate, caprate, and caprylate The "superamides" prepared from these esters have excellent foam stabilizing and viscosity building properties that have led to their use in household detergents, cosmetics, shampoos, and other surfactant applications.

Flavors

A new, 4-page folder describing representative number of some of their modern and very true to character flavoring compounds developed by Fries & Fries Inc. Both spray dried and liquid flavoring compounds are listed for the following categories: cake mixes; cookie and cracker mixes; cocktail crackers, chips and crunches; cereals, pie and pudding fillings; toppings, gelatin deserts, ice cream and water ices; bottlers; candy and chewing gum; oleomargarine dairy and cheese foods; icings, fondants, cookie and sandwich fillings. Flavors for such specialty products as pharmaceuticals; cordials, wines and alcoholic beverages; tobacco and the newest types of prepared foods are also listed.

Enzymes

The enzyme approach to fermentation reactions is the fascinating story of the latest issue of Research Comments published by Evans Research, New York City industrial research laboratory. "Understudy for a Microbe" describes how enzymes are rapidly becoming important in replacing classical fermentation methods, and how fermentation is being used as a method of producing enzymes. These new approaches are discussed has having future significance in the production of antibiotics, steroids, beer, whiskey, wine, vinegar and other products. A bright future for industrial biosynthesis is predicted.

Pulverizers

An informative new brochure on jet pulverizers, for the dry pulverizing of materials to micron-size powders, is being distributed by the manufacturers, The Jet Puverizer Company. Grinding, pulverizing and processing action of Jet Pulverizers are described in this brochure. Originally used in the cosmetics, paints, petroleum and chemical processing industries, the pulverizers now process materials so that they often display new physical characteristics—thus making them adaptable for use in new applications.

Fillers

Recently announced: An extended and rounded out line of high speed automatic liquid filling machines. This equipment is being used with satisfactory results in the drug, cosmetic, chemical and allied industries, according to Popper & Sons, Inc.









MAX FACTOR-1

Max Factor's new "Goldfire" lipstick is being introduced this fall in a box topped with a design of bright flames to catch the eye with a "do-it-yourself" sorcery theme. The two lipsticks provided, Goldfire Red and Golden Frost, are supposed to be blended by the wearer to achieve the "Goldfire" shade. With the lipsticks comes a Max Factor Hi-Society oval mirror-case. The entire set will retail for \$1.95, plus tax.

BOURJOIS-2

Bourjois presents a wide variety of gift sets containing its Evening in Paris line, one of which is pictured. The sets include cologne, cologne sticks, metered spray, talcum powder and other products. The sets are priced from \$1.00 to \$25.00.

BRISTOL-MEYERS-3

To introduce Ipana Plus, Bristol-Myers called upon Contemporary Ceramics of Chathan, New Jersey to create an unusual ceramic piece for distribution among food and drug buyers. The result was this "3-D" ash tray. A year after the original promotion a spot check determined that a good proportion of the recipients are still using the Ipana Plus ash tray.

HELENE-CURTIS-4

In a campaign to attract new users and more repeat business Helene Curtis is reducing the price of the \$1.35 size of GayTop to 99¢. The offer establishes a "once-a-year special" which the company hopes will give an added impetus to sales of this aerosol-packaged "Lanolin Discovery" hairdressing during the hair-problem months of the summer. Magazine advertising launches the special, and combination shelf talkers and stacking cards reflect the advertising at point of purchase. Ad mats to tie-in with local advertising and labels and cartons also spotlight the offer.



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HAZEL BISHOP-5

The Ultra-Matic Show Case, a new lipstick merchandiser designed to attract customers and promote sales of Hazel Bishop lipsticks is pictured above. The counter display cases are being offered to retailers free of charge as part of an offer introducing the company's new line of refillable lipsticks. The case is made of gleaming, transparent Plexiglas acrylic plastic and holds up to six dozen lipstick refills and three dozen master Ultra-Matic cases. It also displays six different lipstick cases and a colorful shade chart. The cases are being made by Just Plastics, Inc. and Lane Displays. The Plexiglas is a product of Rohm & Haas Company.

CARMEL MYERS-6

Carmel Myers presents "Pour Madame et Monsieur," a specially packaged Christmas gift of eau de toilette. Gamin, "a thousand roses in bloom," in a gold aluminum bottle for her; and Zizanie, "aura of lemon trees" in its silver bottle for him, packaged together in a clear plastic case. The set retails for \$17.50.

LITTLE LADY-7

Three new gift sets are announced by Little Lady. All are boxed with an inset of a framed picture of Little Lady ready to be attached to the wall of a child's room. The set pictured is the "Bath Time Set" containing body powder, bottles of scented toilet water and cologne, a cake of sculptured rose soap, and six bath packets. It retails for \$2.50.

CUTEX-8

Gift units set in a colorful display packer by Cutex are suggested as "stocking stuffers" or as tree decorations, bridge prizes and party favors. The deal contains six pieces of an assorted trio of Cutex Pearl Polishes and three pieces of a trio of Cutex Delicate Lipsticks. The packages are multi-colored foil. The sets are available only in the packed deal.





August, 1959





Madame Helena Rubinstein arriving at the Ukraine Hotel in Moscow, USSR. Madame Rubinstein spent a week in the Soviet capital. During this time she opened her Beauty Klask (on July 25th) at the American National Exhibit held in Sokolniki Park, located on the outskirts of the city. She is pictured in one of the limousines provided for each visiter by the Intertourist Bureau—for three hours a day.

Helena Rubinstein Writes From Moscow

"Full of life and people . . . and very hot!" These were Helena Rubinstein's first impressions of Moscow at the opening of the American Fair in Sokolniki Park, where she supervised the beauty pavillion which was her contribution to the American-Russian exchange. Her trip also included an observation of Russian use of beauty products, and a visit to the Moscow Institute of Medical Cosmetics.

Madame Rubinstein, writing from Paris, recalls that her last visit to Moscow was twenty years ago, and this year she found the city and its inhabitants considerably changed. "There are improvements on all sides. The people are not badly dressed. They don't seem to be short of anything."

Cosmetic Use Subdued

The Russian woman's use of beauty products, however, is much more subdued than that of her American counterpart. "When they use cosmetics," Madame Rubinstein reports," they are very light: a touch of lipstick, powder, and that's all."

This abstinence seems due more to unavailability than to lack of enthusiasm. Visting GUM, Moscow's largest department store, Madame Rubinstein noticed that "the few preparations on display are very basic. There are for instance only two different lipsticks available. There are no treatment products. Makeup is reduced to powder. Perfume is in great demand. A universal favorite, so I am told, is 'Krasny Moskva' (Red Moscow). . . Beauty Counselors don't exist. There is a crying need for them."

And a crying interest too, it seems, since the Helena Rubinstein beauty pavillion has been constantly swamped with eager observers since the opening of the fair. The three beauty counselors, Madame Rubinstein reports, are busy all day with hundreds of queries and requests for leaflets as they give their demonstrations. "In addition," she adds. 'daily demonstrations are given on the closed-circuit colour TV, which is viewed by tens of thousands. I watched the first of these, and although they certainly help visitors to know just what is going on, they don't seem to lessen the density of the crowds."

Visits Cosmetic Institute

Madame Rubinstein also visited the Moscow Institute of Medical Cosmetics. "The work done there," she writes, "is extremely scientific and I felt that greater stress is laid on disfigurement than on beauty care."

The director of the Institute, Mr. Kurkovsky, is a highly skilled plastic surgeon. He told Madame Rubinstein that his laboratories analyse samples of each new Helena Rubinstein product and learn from American experiences.

Exchanges Promised

The Institute is barely five years old, but carries the responsibility for the quality of all cosmetics manufactured in the Soviet Union. Madame Rubinstein relates that Mr. Kurkovsky expressed interest in sharing his discoveries and innovations with her in the hopes that in return his new institute could learn from a company experienced in cosmetic research. He and another doctor from the Institute visited the pavillion at the fair and agreed to exchange booklets and other literature with the American beauty experts.

In conclusion Madame Rubinstein states, "It is good to know how well the Exhibit is being received, and in particular to have seen for myself the great popularity of my Beauty Kiosk with the Moscovites."

Only Cosmetic Firm

Helena Rubinstein is the only cosmetic firm participating in the American National Exhibition, covering an area of over 400,000 square feet, which opened on July 25 and will run for six weeks in the Sokolniki Park of Moscow this summer.

Madame Rubinstein was present in person for the inauguration.

The entire beauty program at the Fair is in charge of her niece, Mala Rubinstein, who heads the Rubinstein salons in America. She is assisted by three carefully chosen girls who speak Russian and are thoroughly grounded in the Rubinstein technique.

A beauty salon, representative of those run by Helena Rubinstein in the United States and many other parts of the world, has been set up at the Fair. Here, the care of the skin and the art of make-up are demonstrated daily to visitors.

The Rubinstein treatments are also shown on a closed circuit of color television which covers all areas of the Exhibition.

Provides Make-up

Daily fashion shows, for which makeup of the models is done by the Helena Rubinstein services, are integrated with special beauty demonstrations, following on the same platform at the close of the

Skin care and make-up for the American hostesses at the Fair is furnished by Helena Rubinstein, each young woman (Continued on page 57)



Part of the Graduating group of Rutgers perfumery and essential oils class having dinner at the Military Park Hotel, Newark, June 22nd.

Rutgers Graduates Perfumers

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In answer to the question that is often asked: Whether a good perfumer is born or trained, the Rutgers Extension Center, Newark, N.J., believes it has some clues to the answer, since it has offered evening courses in the chemistry identification and compounding of perfume materials for over two years.

At a graduation dinner held late in June at the Military Park Hotel, fourteen students who completed a full year of study in this specialized program were presented certificates by Dr. Peter A van der Meulen, Director of the Rutgers School of Chemistry.

A short talk was given by Mr. Steffen Arctander, perfumer for van Amerigen-Haebler, New York, who teaches the

Perfumery and Essential Oils course. Mr. Arctander reported that several of his students in a recent exam were able to identify 85% of unlabelled materials Many others showed outstanding ability to combine perfume materials with imagination and purpose. A total of 74 students have been enrolled in this program.

Those students who received certifi-cates were Jean Louis Martin, Edward Davidson, and B. T. Bush, Jr., of Hoff-mann-LaRoche, Inc.; Joseph Yurko, Alfred Helleland, and Peter Munger of Colgate-Palmolive Co.; Otto Linke and Philip Bennato of Trubek Laboratories; Charles Wellenkamp of Fritzsche Bros. Inc.; Frank Rowens of van Dyk Co.; Walter Roy of Lever Bros. Co.; Richard Riso of Maywood Chemical Co.; William Trainor of Hutchinson Co.; and Josef Haus of S. B. Penick & Co.

(Continued from page 56) guide receiving a complete beauty kit— a Harlequin box containing 14 items—

for individual use.

Russian women are welcomed by the firm, for personal consultations or group demonstrations. A distribution of 100,-000 Russian language pamphlets per week provides basic instruction for skin and body care.

SEMI-ANNUAL EDITORIAL INDEX NOW AVAILABLE

The semi-annual editorial index of AMERICAN PERFUMER AND AROMATICS for the period from January 1 through June, 1959 is now available. Copies may be obtained without charge by writing to:

AMERICAN PERFUMER AND AROMATICS

48 West 38th Street New York 18, N.Y.

American Home Products Sales Rise

Sales and earnings of American Home Products Corp. for 1959 are expected to run 10% to 12% ahead of last year's level. At this rate, net for the year might reach \$6.10 a share, up from \$5.53 last year. The diversified producer of ethical and proprietary drugs, foods, cosmetics and household products earned \$42,435,-683 in 1958 on sales of \$402,133,504.

Rexall Acquires IMCO

The Injection Molding Company, known as IMCO, a manufacturer of plastic containers, has been acquired by the Rexall Drug and Chemical Company for an undisclosed number of shares of Rexall stock, Justin Dart, Rexall president, revealed during July.

Dart reported that William Archer,

president of IMCO, will continue as active head of the firm.

"This is an entirely new venture for us," Dart said. "Our chemo-plastics divi-

sion has not previously been engaged in the plastic bottling field."

IMCO headquarters is located in Kansas City, Missouri.

Fritzsche Re-locating **Philadelphia Office**

Fritzsche Brothers, Inc., New York essential oil and chemical firm has announced that on August 5th their Philadelphia Office, formerly located at 12 South 12th Street moved to 7 Wynnewood Road, Wynnewood, Pa. The telephone number of the new office will be TRinity 8-7030. James H. Shumaker, Manager, and Robert Hughes represent Fritzsche Brothers in the Philadelphia area. It is their feeling as well as that of their management that with industry's increasing trend toward de-centraliza-tion, both the firm and its customers will be benefited by this re-location of its Philadelphia service headquarters.

Sixth Annual Cosmetic

The Sixth Annual Cosmetic Seminar of the Society of Cosmetic Chemists will be held in New York on September 23rd and 24th, with the sessions at the French Institute, 22 East 60th Street, New York, and the social phases at the New York Academy of Sciences, 2 East 63rd Street, New York.

A program on the highly controversial and very important subject of "Percutaneous Absorption" has been arranged by Dr. Everett L. Saul, Chairman of the Seminar Committee. Divided into four sections, the program will be as follows:

September 23, 1959 8:00-9:00 A.M.—Registration — French Institute, 22 East 60th Street, New York

METHODS FOR MEASURING PER-CUTANEOUS ABSORPTION

Chairman: Everett L. Saul, Ph.D. 9:00-9:20: Dr. Everett L. Saul On Examination of the Goals of the Cosmetic Manufacturer.

9·20-10:10: Dr. Irvin H. Blank Statement of the problem; definition of terms; critical review of past meth-

10:10-10:30: Coffee Break 10:30-11:15: Dr. Kenneth M. Wilson New methods for measuring absorp-

11:15-11:45: B. Choman Application of Auto-Radiography to the Study of Percutaneous Absorption.

11:45-12:30: Panel: Blank, Choman, Griesemer, Higuchi, Saul, Wilson LUNCHEON: 12:45-1:45 New York Academy of Sciences AFTERNOON SESSION

September 23, 1959 FACTORS WHICH INFLUENCE PER-CUTANEOUS ABSORPTION Chairman: Irvin H. Blank, Ph.D.

2:00-3:00: Dr. R. D. Griesemer Biological factors

3:00-4:00: Dr. T. Higuchi Physico-chemical factors 4:00-5:00: Panel: as above

5:45: Cocktails-New York Academy of

(Continued on page 58)

6:15: Dinner—New York Academy of Sciences

September 24, 1959
DESIRABLE EFFECTS RESULTING
FROM PERCUTANEOUS ABSORPTION OF COSMETIC CHEMICALS
Chairman: Paul Lauffer, Ph.D.

9:00-9:45: Dr. Max A. Goldzieher Estrogens

9:45-10:30: Dr. Frederick D. Malkinson Steroids

10:30-10:45: Coffee Break 10:45-11:45: Dr. Val Cotty

Salicylates 11:15-11:45: Dr. Saul Rubin

Vitamins 11:45-12:30: Panel: Cotty, Rubin, Gold-

zieher, Malkinson LUNCHEON: 12:45-1:45 New York

Academy of Sciences
September 24, 1959
POSSIBLE TOXIC EFFECTS RESULTING FROM PERCUTANEOUS

ING FROM PERCUTANEOUS ABSORPTION OF COSMETIC CHEMICALS

Chairman: Raymond R. Suskind, M.D. 2:00-2:40: Dr. Raymond Suskind Methods for predicting toxic reactions.

2:40-3:20: Dr. Donald J. Birmingham Survey of some cutaneous toxic reactions caused by cosmetic chemicals. 3:20-3:30: Break

3:30-4:00: Dr. L. J. Vinson
Toxic reactions from penetration of
surfactants and metals.

4:00-4:30: Speaker not yet chosen Percutaneous toxicity of cosmetic material

4:30-5:00: Panel: Birmingham, Suskind, Vinson

Hooker Chemical Has Severe Explosion

A severe explosion in a chemical processing building at the Niagara Falls, N. Y., plant of Hooker Chemical Corporation on July 22 killed one employee and caused damage set at approximately \$200,000 as a preliminary estimate. The cause of the accident, now being studied by a plant investigating committee, may not be determined or conjectured for several days.

Warehouse stocks of the chlorinated organic chemicals manufactured in the destroyed building are expected to be adequate to supply customers without interruption until the processes can be started up again elsewhere in the plant within approximately 30 days. Other processes were unaffected except that operations in the adjacent area were shut down temporarily as a safety precaution.

No one was in the building itself at the time of the explosion but two employees fairly near the building were treated for shock while the body of Edward M. Zaczek, 38, an electrician in the maintenance department, assigned to do some repair work in the building, was found about 30 feet from the building, having been hit by flying debris and burned by the fire after the explosion. Mr. Zaczek is survived by his wife, Helen, and five children.

The one-story 50 x 100 ft. concrete block building was demolished. The blast was telt throughout the plant and many windows were broken in other buildings, even several hundred yards

from the explosion.

The last major explosion of this type in a Hooker plant occurred in 1948 at Niagara Falls when one man was killed and three were injured.

Shulton Introduces Astringent For Disturbed Skin— Bid For Teen-Age Market

Based on the successful results of a series of test markets, Shulton is launching a full-scale campaign directed at the teen-age market beginning September 1st with full pages featuring the product in leading magazines. Particular emphasis will be placed on teen-age and college publications. A spot radio campaign in 45 major markets will be directed at the rock and roll set through disk jockeys, and both national and co-op advertising will run in metropolitan newspapers coast to coast.

National publicity will be released, and a special tie-in with Seventeen Magazine's Beauty Workshop will perform an educational service through teen-age beauty classes held in better department stores across the country.

Walker Announces Consolidation

International Flavors & Fragrances Inc. announces the consolidation of its domestic headquarters for ALVA and P&S flavors at its Elizabeth, New Jersey location. Flavor manufacturing operations

B-W LANOLIN U.S.P.

EVENTUALLY-For better creams, with economy

B-W Lanolin the superior quality puts into your cream that which gives the skin that smooth soft velvety feeling.

B-W Lanolin will never cause your cream to darken, is best by test and contains over 15% free and combined Cholesterol.

No other base used in your cream, equals the merits of B-W Lanolin. B-W HYDROPHIL (Absorption Base) Made in U.S.A.

BOPF-WHITTAM CORPORATION

America's Original Lanolin Producer Established 1914 Executive Office, Laboratory and Factory: Linden, N.J.



Distillers of essential oils of outstanding quality. Exclusive American agents for genuine

MYSORE SANDALWOOD OIL



R. D. WEBB & CO., INC.
Main Office: Cos Cob, Conn. Branches: Chicago and Los Angeles



will continue as before at Teterboro and Union Beach, New Jersey, as well as at Flizabeth.

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International Flavors & Fragrances Inc. was formed six months ago through the merger of van Amerigen-Haebler of New York and Polak & Schwarz of the Netherlands.

According to Charles P. Walker, President of International Flavors & Fragrances Inc., this consolidation is a logical development that is expected to improve operating efficiency and provide better customer service. "With our newly combined facilities," Mr. Walker stated, "we look forward to an expanded research program, more intensive product development for customers, and improved manufacturing efficiency. We have expanded our domestic sales activities to take advantage of the positive features that will develop from this program of consolidation."

At the same time, the company announced a new and distinctive label to be used for its flavor materials. It emphasized that label designations and numbers for both ALVA and P&S flavors will continue unchanged.

Avon Reports Record Sales

Sales and earnings of Avon Products, Inc. and subsidiaries were at record levels for the first six months of 1959 according to a report issued late in July by John A. Ewald, president.

Consolidated net sales for the six months ended June 30, 1959 totaled \$59,-

615,124, an increase of 22.4 per cent over sales of \$48,720,693 reported for the comparable 1958 period.

Net earnings after taxes for the first half of 1959 reached \$5,658,372, a 64.1 per cent increase over net earnings of \$3,447,212 in the similar 1958 six months. The 1959 earnings were equal, after preferred dividends, to \$1.77 per share based on the 3,178,091 shares outstanding at June 30, 1959, and compare with \$1.07 per share for the first half of 1958 calculated on the same number of outstanding shares.

According to Mr. Ewald, the higher level of sales resulted from the increasing acceptance accorded Avon's line of cosmetics and toiletries. This, coupled with aggressive merchandising and new product introductions, puts Avon in a very favorable position, he stated. "The marked improvement in earnings over the comparable 1958 period," he said, "reflects the fact that the increased sales volume was attained without a proportionate rise in manufacturing and distribution costs, but with a more profit-

Third Beautyrama Exhibition Planned

able product mix."

The Philadelphia Inquirer will present its third annual Beautyrama cosmetic exhibition for consumers in the grand ballroom of the Sheraton Hotel, Philadelphia, on September 9, 10 and 11.

Highlight of the three-day presentation will be an international fashion show

with performances twice daily. In addition to displays and demonstrations, beauty clinics and lectures will be held each day.

Among the firms planning exhibits are:
Max Factor, Prince Matchabelli, Simonetta Perfumes, Coty, Bonne Bell, Lydia
O'Leary, Norelco, Lilly Dache, Marie
Early, Sardeau, Roux, Elizabeth Arden,
Helena Rubinstein, Dana Perfumes, Parfums Caron and "His" Toiletries for Men.

Second International Essential Oil Congress Meets at Grasse

The Second International Congress on Essential Oils, succeeding the first which was held at Reggio Calabra in 1956, met at Grasse July 23-25.

The National Union of Producers of Essential Oils of Grasse arranged the program of the Congress, making it well-rounded as well as practical by including, in addition to scientific meetings devoted to the constitution of essential oils, tours of the plants, excursions into the areas of cultivation around Grasse, informal discussions, and trips to the tourist sites nearby.

The delegates came from all parts of the world including the Far East and areas behind the Iron Curtain. They were joined by technicians from all over France.

Among the visiting speakers were: Prof. L. Ruzicka, Nobel Prize winner from Switzerland; Dr. C. Scholtens, from Holland; Dr. Y. R. Naves, from Switzer-





land; Prof. Ivanoff from Bulgaria; Dr. Tucakov from Yugoslavia; Dr. Herout from Czechoslovakia; Prof. N. Iakobachvili from Russia; Prof. Sadgopal from India; and Dr. Treibs from Germany.

The major aim of the Congress was to achieve an enlarged acquaintance and a comparison on the part of the delegates of research and methods in use in various parts of the world. It was felt that if some constants should be established in an attempt to standardize essential oil products, it is important to take into account factors which modify the odor of certain floral products.

And it is this consideration which should lead researchers to study more precisely the biogenesis of aromatic derivatives, keeping in mind the structures of their origins, variations of soil, the influence of atmospheric elements, and any other particular factors which might apply, said a Congress spokesman.

It was felt that the fundamental studies at the basis of this research could only be valuably undertaken if they were part of an integrated program extending beyond national limits. It was hoped that the comparison at an international level of these various research projects would help answer at least in part the questions of both producers and consumers. This end of course can only be achieved by successive stages; the organisers of the Second International Congress hope that the meetings they arranged will prove of value to the growth of this knowledge.

Breck Survey Shows Continuing Market For Hair Preparations

Results of the 12th and latest annual hair care survey conducted by John H. Breck Inc. point up the fact that from a statistically balanced cross-section of American women, four out of five described themselves as having one or

more hair problems.

Survey figures supporting this existence of a continuing vast market for hair care preparations indicate that one out of three women complain of dandruff and manageability problems, while three out of every ten women claim to have hair that is too dry. Other hair problems reported included hair too oily, hair lacking lustre, and falling hair.

Seven out of ten women questioned

during the survey admitted to having some degree of gray in the natural color of their hair, and 28% of all women interviewed had some type of hair coloring treatments during the period covered by the Breck Survey. Such treatments were predominantly the "rinse" however.

Two out of three women described their hair as straight, and less than one out of four claimed to have naturally

blonde hair.

The continued decline in popularity of home permanents was proven by the survey which reported that while 33% of the women interviewed used one in 1957, only 27% used one in 1958.

Edward J. Breck, President of the firm conducting the survey, stated that he and his firm views the future business potential for hair care preparations with great optimism. However, he pointed out that the greatest advances would be made, in his opinion, by preparations that afford consumers real "convenience" in terms of ease of use and time-savings.

Colgate-Palmolive **Earnings Up**

The Colgate-Palmolive Company six months earnings and sales announced in July exceeded the high levels established last year

Consolidated net income for the first six months of 1959 was \$11,085,000 or \$1.37 per share of common stock, an increase of \$2,730,000 or 33% over earnings of \$8,355,000 or \$1.08 per share in the comparable period of 1958.

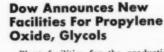
Consolidated sales for the first six months established a new record of \$292,216,000 as compared with \$265,-446,000 for the same period in 1958, an increase of \$26,770,000 or 10 per cent.

For the second quarter of 1959, consolidated earnings were \$6,079,000 or 75 cents per share as compared with \$3.935.000 or 51 cents in the same quarter of last year.

Consolidated sales of \$150,556,000 for the second quarter also established a new quarterly record, increasing \$13,416,000 over the \$137,150,000 for the second

quarter of 1958.

Earnings per share are based on an average of 7,960,000 shares outstanding in the current year and 7,511,000 shares in the preceding year.



Plant facilities for the production of propylene oxide, propylene glycol and dipropylene glycol have been completed by The Dow Chemical Company at its Louisiana Division at Plaquemine.

Dow is the only chemical company producing these products at more than one location. Dow manufactures propy-lene oxide at its Midland (Michigan) Division and Texas Division in Freeport. Propylene glycol also is produced at Dow's Texas Division.

These products find use as basic raw materials or chemical intermediates in the automotive, food, pharmaceutical, paper, cosmetics, soap, textile, plastics, rubber, tobacco, and chemical process industries.

Dow said the Plaquemine facility was a further "guarantee of our capacity to produce and our ability to deliver in the quantities required by our customers.

Soap Fraud Curtailed

A Winnipeg man who sold housewives concoction of cheap soap and borax under popular brand names was given a two-year suspended sentence in police court

Police said Modest William Sklepowich, 26, had a thriving business, with telephone girls contacting housewives before police were tipped off by the Better Business Bureau late last year.

Court was told the women were asked what brand of soap they used, then were offered the same brand at reduced rates. No matter what brand they used, they got the same mixture prepared in Sklepowich's basement, and packed in plastic

Sklepowich, a graduate pharmacist, conducted the soap business for about

two months.

He was also fined \$100 for publishing a false advertisement. He mailed circulars to businessmen soliciting advertising space in a non-existent magazine, Opportunities Illustrated.

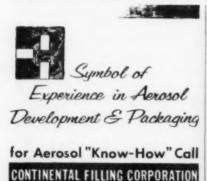
No one accepted his offer.

Texas Pharmacal Upheld

Texas Pharmacal Company, owner and holder of "Allercreme" and "Saf-Tan" trademarks filed petition against Aloe-Creme Laboratories of Fort Lauderdale, Florida, for cancellation of its registration, "Aloe-Creme", and opposed its application for registration of "Aloe-Creme After-Tan"

In April of 1958 the Examiner of Interferences for the United States Patent Office sustained the position of Texas Pharmacal Company in both respects, that is, (1) the petition to cancel the registration, "Aloe-Creme", was granted and (2) the registration of the mark, "Aloe-Creme After-Tan", was refused.

Aloe-Creme Laboratories, Inc. appealed the decision to the Commissioner of Patents and on July 10th, 1959, by written opinion the decision of the Examiner of Interferences was in all things sustained



123 N. Hazel . Danville, Illinois



and affirmed, thus upholding Texas Pharmacal.

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Hercules Powder Company reported for the six months ended June 30, 1959, net income equal to \$1.36 a share of common stock.

Net income in the first six months of 1958 was equal to 89 cents a share of common stock.

For the second quarter of 1959, net income was equal to 79 cents a share of common stock. This compares with net income in the second quarter of 1958 equal to 51 cents a share.

Net sales and operating revenues for the six months' period were \$137,200,-312, compared with \$116,773,028 for the corresponding 1958 period.

U. S. Cosmetics To Be Honored By French

American-made cosmetics will be honored with the award of the coveted "Grand Prix" according to M. Jules du Bois Lambert, Secretary General of the Comite du Grand Prix Americain. The first awards will be made in Fall 1959.

Speaking at a press reception at the Ritz Hotel in Paris M. Lambert said, "The Comite feels that manufacturers of American cosmetics have incorporated in their products and in their advertising the spirit of 'savoir faire' that we French consider so important in our daily lives. Moreover, the beauty aids developed in America have been a boon to women all over the world."

The Comite du Grand Prix Americain was founded to honor American industry for its contributions to better living and to world-wide industry. Among the other product categories in which awards will be made are automobiles, men's and women's fashions, beverages, appliances, home furnishings and others. The Comite will meet on a quarterly basis in its head-quarters in the Ritz Hotel. At these meetings products nominated will be evaluated by the Comite with the help of a staff of technical advisers. Actual presentation of the awards will be made at special receptions in the United States attended by dignitaries of Franco-American social, civic and business life.

Barr Shelf-Tests 15,000th Container

Stability testing of aerosol products at G. Barr and Company, aerosol formulators and producers, reached a milestone this week when the 15,000th container was entered in the firm's Chicago laboratory shelf room for shelf time evaluation. The stability testing is part of the company's overall quality control system.

Since the shelf test procedure was instituted four and one-half years ago, four containers of every run of every aerosol product made by the company have been shelved; then one of the four containers is tested at intervals of one month, six months, one year, and four years after the date of production.

Barr's technical director, Morris J. Root, reported that each interval test includes checks for weight loss, valve operation, corrosion, product function, odor and color. Identical testing is performed in the company's New York plant laboratory.

Root pointed out that findings of the tests over the past few years have produced data useful in the formulation of new products as well as in extending the shelf life of existing products. Temperature and humidity controls in the shelf room simulate the range of atmospheric conditions in retail store and household storage.

The shelf time testing, Root said, has proved valuable in corroborating laboratory prediction tests for corrosion. These tests, applied during product formulation, include: 1) oven testing which speeds up corrosion causing conditions; 2) iron and tin analysis tests, and 3) electrolytic cell tests to measure current flow between an aerosol product and metallic components of containers.

Genie Sued By Jeenie

August 24 has been set as the date for trial, in U.S. district court in San Francisco, of a trademark infringement suit involving Colgate-Palmolive Company's Genie detergent and the Jay S. Conley Company's Jeenie cleansing product, according to Advertising Age. The suit against Colgate was filed on behalf of Conley, a Mountain View, Calif. manufacturer, by Anthony Diepenbrock, an associate of Townsend & Townsend, San Francisco attorneys.

Judge Willis W. Ritter heard arguments July 6-7 on a motion presented by Mr. Diepenbrock for a preliminary injunction which, if granted, would have halted distribution and sale of Colgate's Genie. At this hearing, Mr. Diepenbrock said, "We agree to the court's proposal for an early trial." Attorneys for Colgate argued they would need a minimum of six months in which to prepare for trial.

The motion for a preliminary injunction remains "alive" despite the setting of the August trial date, and the judge who hears the case could, at his discretion, grant the motion and issue an injunction even while the trial is in progress.

Colgate, in turn, has filed a counterclaim (not a countersuit) which, in effect, is a move to offset the Conley claim that Colgate infringed the Jeenie trademark by the distribution of its Genie heavy-duty detergent. In the counterclaim, Colgate alleged, in essence, that Conley's use of the Jeenie label did not constitute a trademark usage until after April 1, 1958, by which time Colgate's Genie had been on the market.

Thus Colgate asserts that Conley used its trademark later than Colgate and, in effect, infringed the C-P trademark.

Mr. Diepenbrock went to New York, Boston and Washington in July to take depositions which will be used in the August trial

Mr. Diepenbrock also stated that Conley will seek monetary damages, although it is impossible at this time to determine the amount of loss in potential sales of Jeenie caused by the introduction of Genie.





MODEL EBW PORTABLE FILTER—This filter is recommended for small capacity requirements. Accomodates from 4 to 8 124" dia. filter disks. Easy to set-up and operate.



Will rapidly fill small or batch lots of material at lowest cost. Fills bottles to uniform height without loss of material. Interchangeable spouts for filling shaker-type bottles to gallons.



Ertel Asbestos Filter Sheets for ultra polished brilliance are used for many fine perfumes and cosmetics. Available in 10 grades to fit all standard filters. Write regarding samples for superior result tests in your filter.

Write for Illustrated Catalog





Rose M. Harten has been named director of public relations for Chanel, Inc. Her responsibilities will include developing and coordinating consumer, trade and media relations, and product promotion



Rose M. Harten

and information. Miss Harten comes to Chanel from the public relations firm of Hill & Knowlton, Inc., where she was in charge of the public relations activities of the Fragrance Foundation.

Edward D. Alper has been named a vice president of the Nepera Chemical Co., Inc., a subsidiary of Warner-Lambert Pharmaceutical Company. He has been plant manager of Nepera since 1957.



C. Ray Sanders

C. Ray Sanders has been appointed manager of the West Coast Division of International Flavors & Fragrances, Inc. Mr. Sanders will administer the West Coast Branch of the company and direct sales operations of the van Ameringen-Haebler and Polak & Schwarz Divisions in eleven western states. Mr. Sanders has previously been with the Rexall Drug Company. He is currently first vice president of the California Cosmetic Association.

Dr. Chester L. French, head of the quality and related problems group of the department of chemical control of Mallinckrodt Chemical Works has been elected chairman of the labels and precautionary information committee of the Manufacturing Chemist's Association, Inc.

George D. Selden has been appointed New York district sales manager for the plastic container division of Thatcher Glass Manufacturing Company, Inc. Mr. Selden comes to Thatcher from Vick Chemical Company where he was director of market and product research for the extruded plastics division.

Frank E. Riley became, on July 9, the only living member of Fritzsche Brothers, Inc. to have completed a total of 50 years in its service. In recognition he was presented with a gift of government securities by President John L. Cassullo on behalf of the firm's officers and directors.



B. Fainberg

B. Fainberg has been appointed export manager of the international division of Dragoco, Inc. For the past nine years Mr. Fainberg has been in charge of the export departments of Roure-Dupont, Inc. and its affiliate Floramatic, Inc.

Pete Jouflas has been appointed sales representative for the states of Washington and Oregon for Prince Matchabelli. Mr. Jouflas has represented Revlon in the west for the past three and a half years.

Robert Granitz has been appointed vice president and general manager of the Alexandra de Markoff Sales Corporation, a subsidiary of Charles of the Ritz. For the past ten years Mr. Granitz has represented Charles of the Ritz in the southeast

Edgar W. Nelson has been named to the newly created post of general manager of the Lehn and Fink Division of Lehn and Fink Products Corporation. Mr. Nelson has been senior vice president of



Edgar W. Nelson

the Market Planning Corporation, an affiliate of McCann-Erickson, Inc. since 1956. In his new position Mr. Nelson will take on the direction of the division's overall administration, including sales, merchandising, advertising and promotion. Before joining the Market Planning Corporation, Mr. Nelson was assistant to the president of Lever Brothers Company.



Ira B. Kap

Ira B. Kapp, technical director of the Felton Chemical Company attended the International Congress held in Grasse, France, July 22-25. He was accompanied by Mr. Leon Gefen of the company's Versailles branch.

Ambrose Y. Frantz, plant manager of Turner Tube Corporation, has been elected vice-president of the firm. Mr. Frantz has been active in the tube industry since 1931.



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George Liebel has been named manager of the Canadian Division of Felton Chemical Co. A chemistry major from the University of Leeds, England, Mr. Liebel joined Felton's Montreal office in 1944, transferring to sales in 1948.

Richard H. McCarthy Jr. has been appointed director of sales for the Bradley-Sun Division, American Can Company.
Mr. McCarthy will direct sales of the division's product line of collapsible metal and plastic tubes, plastic bottles, aluminum impact extrusions and other items.



Bill Rowells

Bill Rowells has been appointed the director of a newly established package design department at Helene-Curtis-Lentheric. Mr. Rowells joined Helene Curtis in 1952 and was named art director in 1957. In his new position he will be responsible for the creative development of new packaging for all Helene Curtis-Lentheric products.

Charles H. Shields, Jr. has been named supervisor of new product development at Heyden Newport Chemical Corporation. He will be responsible for coordinating all activities relating to initial marketing of new products. Mr. Shields has been engaged in market development for the company's newer organic chemicals since 1957.

Alastair B. W. Anderson has been appointed a product manager of Shulton, Inc. He will plan and coordinate the marketing and merchandising program for Bronztan, Thylox Medicated line, Ice-O-Derm and other new products. Robert V. Knapp has been appointed a sales representative for the Fine Chemicals Division in the eastern area.

Lawrence F. Heileman has been named managing director of the cosmetic and aerosol divisions of the Risdon Manufacturing Company with responsibility for sales and manufacturing activities. Mr. Heileman has been manager of the firm's Danbury plants for the past three years. Edward Noyack, factory manager of the Naugatuck plant, is new managing director of the Naugatuck and Waterbury plants, responsible for their manufacturing and engineering operation. Donald S. Tuttle, Jr., presently sales



Lawrence Heileman

manager of the aerosol division, has been made sales manager of the cosmetic division as well. Raymond W. Wolff, who for eleven years has served in several Risdon divisions as a sales and design engineer, was named product development manager of the cosmetic and aerosol divisions.

Wallace G. Brindise has been made general sales manager of R. D. Webb & Co., Inc. John Yuille has joined the company as comptroller. Benjamin J. Jarvis, formerly vice president of sales, has been appointed vice president in charge of production at the Linden, N. J. plant. A. Rolph Evans, formerly in charge of manufacturing, is now vice president of research and development there.

Robert R. Musser and Victor C. White have been elected assistant treasurers of the Rexall Drug and Chemical Company.



William Lyons

William Lyons has been appointed advertising manager of the U.S. division of Max Factor and Co. Before joining Max Factor Mr. Lyons was with the Toni Company as brand manager and before that, with Benton & Bowles, Inc. as an account executive.



Frank W. May

Frank W. May has been named vice-president and general manager of Ans-bacher-Siegle Corporation, a division of Sun Chemical Corporation. Mr. May has been associated with Ansbacher-Siegle since 1957, when he joined the company as a plant manager. William V. Machaver, former vice-president of personnel of U. S. Reduction Co., has been named director of personnel of the Sun Chemical Corporation. Mr. Machaver will assist with the personnel development programs for Sun's several divisions.



William V. Machaver

C. Frank Morgan has been elected executive vice president and Raymond Strobl has been elected sales manager of the Albert Verley Company. Mr. Strobl has been with the company for ten years. Mr. Morgan has been controller and treasurer for five years.

William D. Wallace and Lowell H. Smith have been elected vice-presidents of Crown Cork & Seal Company, Inc. Prior to his election, Mr. Wallace was director of manufacturing. Now he will head all of Crown's manufacturing, industrial relations and engineering activities. Mr. Smith, as vice-president, will continue as general manager of Crown's machinery division, a post he has held for the past several years. John L. Carnie, general manager of Crown's can orerations since 1953, will succeed W. D. Wallace as director of manufacturing. Laverne J. Butcher has joined the company as works manager of its closure plant no. 10 in Baltimore. Mr. Butcher was formerly associated with the York Shipley Company as vice-president of manufacturing.

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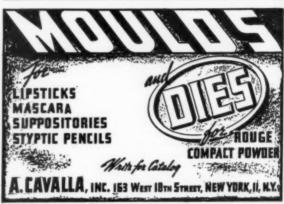
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"Perfumes and Their Production"

By E. S. MAURER

Here is a practical working guide by E. S. Maurer, who has long been regarded as an unrivalled source of information. In part I, the reader is offered a complete picture, not merely of formulation alone, but of the entire industry from the point of view of approach, methods, and technique. Part II is a systematized and highly informative discussion of all the commonly used perfumery isolates and synthetics.

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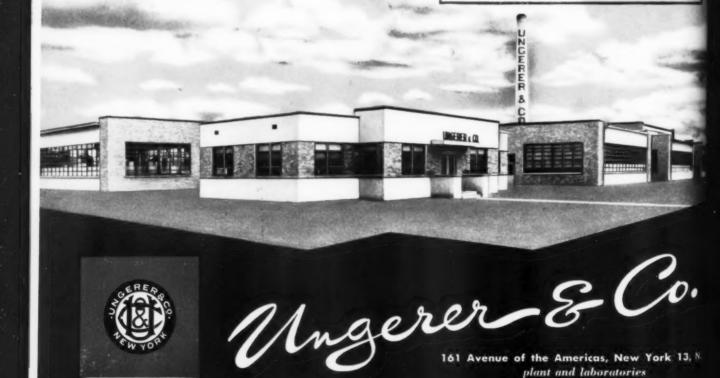
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